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(71) Applicant (<i>for all designated States except US</i>): GENZYME CORPORATION [US/US]; One Mountain Road, Framingham, MA 01701 (US).			
(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): ARMENTANO, Donna, E. [US/US]; 352 Brighton Street, Belmont, MA 02178 (US). GREGORY, Richard, J. [US/US]; 2 Wintergreen Lane, Westford, MA 01866 (US). SMITH, Alan, E. [GB/US]; 1 Mill Street, Dover, MA 02030 (US).			
(74) Agent: SEIDE, Rochelle, K.; Baker & Botts, LLP, 30 Rockefeller Plaza, New York, NY 10112 (US).			
(54) Title: CHIMERIC ADENOVIRAL VECTORS			
(57) Abstract			
<p>A chimeric adenoviral vector is provided that comprises nucleotide sequence of a first adenovirus, wherein all or part of at least one gene of said first adenovirus encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by all or part of the corresponding gene from a second adenovirus belonging to subgroup D, said vector further comprising a transgene operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell. Compositions comprising such vectors and methods of using such vectors to deliver transgenes to target mammalian cells, particularly airway epithelial cells, are also provided.</p>			

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Description

Chimeric Adenoviral Vectors

5. Introduction

The present invention relates to chimeric adenoviral vectors, that is, vectors comprising DNA from more than one serotype of adenovirus, which offer enhanced infection efficiency of target cells in order to deliver one or more therapeutically useful nucleotide sequences, including transgenes, therein. Such a nucleotide sequence may comprise a gene not otherwise present in the target cell that codes for a therapeutic and/or biologically active protein, or may represent, for example, an active copy of a gene that is already present in the target cell, but in a defective or deficient form.

10 15 Background of the Invention

One of the fundamental challenges now facing medical practitioners is that although the defective genes that are associated with numerous inherited diseases (or that represent disease risk factors including for various cancers) have been isolated and characterized, methods to correct the disease states themselves by providing patients with normal copies of such genes (the technique of gene therapy) are substantially lacking. Accordingly, the development of improved methods of intracellular delivery therefor is of great medical importance. Examples of diseases that it is hoped can be treated by gene therapy include inherited disorders such as cystic fibrosis, Gaucher's disease, Fabry's disease, and muscular dystrophy.

20 25 Representative of acquired disorders that can be treated are: (1) for cancers: multiple myeloma, leukemias, melanomas, ovarian carcinoma and small cell lung cancer; (2) for cardiovascular conditions: progressive heart failure, restenosis, and hemophilias; and (3) for neurological conditions: traumatic brain injury.

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Gene therapy requires successful transfer of nucleic acid to the target cells of a patient. Gene transfer may generally be defined as the process of introducing an expressible polynucleotide (for example a gene, a cDNA, or an mRNA patterned thereon) into a cell. In a particular application of this approach, successful expression of an encoding polynucleotide leads to production in the cells of a normal protein and leads to correction of a disease state associated with an abnormal gene. Therapies based on providing such proteins directly to target cells (protein replacement therapy) have generally proved ineffective since, for example, the cell membrane presents a selectively permeable barrier to entry. Thus there is great interest in alternative methods to cause delivery of therapeutic proteins, especially by transfer of the relevant polynucleotide, often referred to as a transgene.

Viral vectors have been used with increasing frequency to date to deliver transgenes to target cells. Most attempts to use viral vectors for gene therapy have relied on retrovirus-based vectors, chiefly because of their ability to integrate into the cellular genome. However, the disadvantages of retroviral vectors are becoming increasingly clear, including their tropism for dividing cells only, the possibility of insertional mutagenesis upon integration into the cell genome, decreased expression of the transgene over time, rapid inactivation by serum complement, and the possibility of generation of replication-competent retroviruses. See, for example, D. Jolly, et al., Cancer Gene Therapy, 1, 1994, pp. 51-64, and C.P. Hodgson, et al., Bio Technology , 13, 1995, pp. 222-225. Such disadvantages have led to the development of other viral-based vector systems, including those derived from adenoviruses.

Adenovirus (Ad) is a nuclear DNA virus with a genome of about 36 kb, which has been well-characterized through studies in classical genetics and molecular biology. A detailed discussion of adenovirus is found in Thomas Shenk, "Adenoviridae and their Replication", and M. S. Horwitz, "Adenoviruses", Chapters 67 and 68, respectively, in Virology, B.N. Fields et al., eds., 2nd edition, Raven Press, Ltd., New York, 1996, and reference therein is found to numerous aspects of adenovirus pathology, epidemiology, structure, replication, genetics and classification.

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In a simplified form, the adenoviral genome is classified into early (known as E1-E4) and late (known as L1-L5) transcriptional units, referring to the generation of two temporal classes of viral proteins. The demarcation between these events is viral DNA replication.

5 The human adenoviruses are divided into numerous serotypes (approximately 47, numbered accordingly and classified into 6 subgroups: A, B, C, D, E and F), based upon properties including hemagglutination of red blood cells, oncogenicity, DNA base and protein amino acid compositions and homologies, and antigenic relationships. Additional background information concerning Ad serotype
10 classification, including that for subgroup D, can be found, for example, in F. Deryckere et al., Journal of Virology, 70, 1996, pp. 2832-2841; and A. Bailey et al., Virology, 205, 1994, pp. 438-452, and in other art-recognized references.

Adenoviruses are nonenveloped, regular icosahedrons (having 20 triangular surfaces and 12 vertices) that are about 65-80 nm in diameter. A protein called fiber
15 projects from each of these vertices. The fiber protein is itself generally composed of 3 identical polypeptide chains, although the length thereof varies between serotypes. The protein coat (capsid) is composed of 252 subunits (capsomeres), of which 240 are hexons, and 12 are pentons. Each penton comprises a penton base, on the surface of the capsid, and a fiber protein projecting from the base. The Ad 2 penton base protein,
20 for example, has been determined to be a 8 x 9 nm ring shaped complex composed of 5 identical protein subunits of 571 amino acids each.

Current understanding of adenovirus-cell interactions suggests that adenovirus utilizes two cellular receptors to attach to, and then infect a target cell. It has been further suggested that the fiber protein of an infecting adenovirus first attaches to a
25 receptor, the identity of which is still unknown, and then penton base attaches to a further receptor, often a protein of the alpha integrin family. It has been determined that alpha-integrins often recognize short amino acid sequences on other cellular proteins for attachment purposes including the tripeptide sequence Arg-Gly-Asp (abbreviated RGD). An RGD sequence is also found in the penton base protein of

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adenovirus and is currently understood in the art to mediate attachment of Ad to alpha integrins.

Recombinant adenoviruses have several advantages for use as gene transfer vectors, including tropism for both dividing and non-dividing cells, minimal pathogenic potential, ability to replicate to high titer for preparation of vector stocks, and the potential to carry large inserts (Berkner, K.L., Curr. Top. Micro. Immunol. 158:39-66, 1992; Jolly, D., Cancer Gene Therapy 1:51-64, 1994).

The carrying capacity of an adenovirus vector is proportional to the size of the adenovirus genome present in the vector. For example, a capacity of about 8 kb can be created from the deletion of certain regions of the virus genome dispensable for virus growth, e.g., E3, and the deletion of a genomic region such as E1 whose function may be restored in trans from 293 cells (Graham, F.L., J. Gen. Virol. 36:59-72, 1977) or A549 cells (Imler et al., Gene Therapy 3:75-84, 1996). Such E1-deleted vectors are rendered replication-defective, which is desirable for the engineering of adenoviruses for gene transfer. The upper limit of vector DNA capacity for optimal carrying capacity is about 105%-108% of the length of the wild-type genome. Further adenovirus genomic modifications are possible in vector design using cell lines which supply other viral gene products in trans, e.g., complementation of E2a (Zhou et al., J. Virol. 70:7030-7038, 1996), complementation of E4 (Krougliak et al., Hum. Gene Ther. 6:1575-1586, 1995; Wang et al., Gene Ther. 2:775-783, 1995), or complementation of protein IX (Caravokyri et al., J. Virol. 69:6627-6633, 1995; Krougliak et al., Hum. Gene Ther. 6:1575-1586, 1995). Maximal carrying capacity can be achieved using adenoviral vectors deleted for all viral coding sequences (Kochanek et al., Proc. Natl. Acad. Sci. USA 93:5731-5736, 1996; Fisher et al., Virology 217:11-22, 1996).

Transgenes that have been expressed to date by adenoviral vectors include p53 (Wills et al., Human Gene Therapy 5:1079-188, 1994); dystrophin (Vincent et al., Nature Genetics 5:130-134, 1993; erythropoietin (Descamps et al., Human Gene Therapy 5:979-985, 1994; ornithine transcarbamylase (Stratford-Perricaudet et al.,

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Human Gene Therapy 1:241-256, 1990; We et al., J. Biol. Chem. 271:3639-3646, 1996;); adenosine deaminase (Mitani et al., Human Gene Therapy 5:941-948, 1994); interleukin-2 (Haddada et al., Human Gene Therapy 4:703-711, 1993); and α1-antitrypsin (Jaffe et al., Nature Genetics 1:372-378, 1992); thrombopoietin 5 (Ohwada et al., Blood 88:778-784, 1996); and cytosine deaminase (Ohwada et al., Hum. Gene Ther. 7:1567-1576, 1996).

The particular tropism of adenoviruses for cells of the respiratory tract has particular relevance to the use of adenovirus in gene therapy for cystic fibrosis (CF), which is the most common autosomal recessive disease in Caucasians. The disease is 10 caused by the presence of one or more mutations in the gene that encodes a protein known as cystic fibrosis transmembrane conductance regulator (CFTR), and which regulates the movement of ions (and therefore fluid) across the cell membrane of epithelial cells, including lung epithelial cells. Abnormal ion transport in airway cells leads to abnormal mucous secretion, inflammation and infection, tissue damage, 15 and eventually death. Mutations in the CFTR gene that disturb the cAMP-regulated Cl⁻ channel in airway epithelia result in pulmonary dysfunction (Zabner et al., Nature Genetics 6:75-83, 1994). Adenovirus vectors engineered to carry the CFTR gene have been developed (Rich et al., Human Gene Therapy 4:461-476, 1993) and studies have shown the ability of these vectors to deliver CFTR to nasal epithelia of CF patients 20 (Zabner et al., Cell 75:207-216, 1993), the airway epithelia of cotton rats and primates (Zabner et al., Nature Genetics 6:75-83, 1994), and the respiratory epithelium of CF patients (Crystal et al., Nature Genetics 8:42-51, 1994). Recent studies have shown that administering an adenoviral vector containing a DNA sequence encoding CFTR 25 to airway epithelial cells of CF patients can restore a functioning chloride ion channel in the treated epithelial cells (Zabner et al., J. Clin. Invest. 97:1504-1511, 1996; U.S. Patent No. 5,670,488 issued September 23, 1997).

Serotype classification is partly based on viral surface protein sequence variation. Because the infectious capabilities of the virus are associated with the surface protein interactions of the virus with cellular proteins, the serotype is an

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important determinant of viral entry into target cells, and can account for the infectious heterogeneity of adenovirus serotypes. Most adenoviral vectors have been constructed using adenovirus serotypes from the well-studied group C adenoviruses, especially Ad 2 and Ad 5. However, other adenovirus serotypes display infectious properties that are relevant to the further design of improved adenoviral vectors, for example, those derived from subgroup D, which display enhanced tropism for human airway epithelial cells.

It is widely hoped that gene therapy will provide a long lasting and predictable form of therapy for certain disease states, and it is likely the only form of therapy suitable for many inherited diseases. Although adenoviral vectors are currently in clinical use and have shown therapeutic promise, a need remains to improve the infection efficiency of these vectors in order to further improve their gene transfer capabilities. The present invention addresses this goal.

15 Summary Of The Invention

The present invention provides for chimeric adenoviral vectors which offer enhanced infection efficiency of target cells for the delivery of one or more transgenes. In a representative aspect of the invention, the vectors comprise nucleotide sequences coding for therapeutically useful proteins and have enhanced tropism for airway epithelial cells.

Accordingly, there are provided chimeric adenoviral vectors comprising nucleotide sequence of a first adenovirus, wherein at least one gene of said first adenovirus encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by the corresponding gene from a second adenovirus belonging to subgroup D. These vectors may further comprising a transgene operably linked to a eucaryotic promoter or other regulatory elements to allow for expression therefrom in a mammalian cell. In a representative aspect thereof, the replaced encoding sequence codes for Ad fiber, hexon or penton base.

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In a further preferred embodiment of the invention, there are provided chimeric adenoviral vectors comprising nucleotide sequence of a first adenovirus, wherein a portion of a gene thereof encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by a 5 portion of the corresponding gene from a second adenovirus belonging to subgroup D. These vectors may further comprising a transgene operably linked to a eucaryotic promoter or other regulatory elements to allow for expression therefrom in a mammalian cell. In a representative aspect thereof, the replaced encoding sequence codes for a portion of Ad fiber, hexon or penton base.

10 Preferably, the second adenovirus is a member of subgroup D, and the replaced nucleotide sequence encodes a polypeptide selected from the group consisting of Ad fiber, a fragment of Ad fiber, Ad hexon, a fragment of Ad hexon, Ad penton base, and a fragment of Ad penton base. In a preferred embodiment, said second adenovirus is selected from the group consisting of serotypes Ad 9, Ad 15, Ad 15 17, Ad 19, Ad 20, Ad 22, Ad 26, Ad 27, Ad 28, Ad 30, and Ad 39. In preferred embodiments of the chimeric adenoviral vectors, the first adenovirus is selected from the group consisting of Ad 2, Ad 5, and Ad 12.

20 The invention is also directed to compositions comprising the chimeric adenoviral vectors of the invention. Additional aspects of the invention include methods to use the chimeric adenoviral vectors of the invention to deliver transgenes to mammalian target cells, for example, to the airway epithelial cells of patients.

A still further representative aspect of the invention involves a method of providing a therapeutic and/or biologically active protein to the airway epithelial cells of a patient by administering to said cells an adenoviral vector comprising elements of 25 an Ad 17 genome, and a transgene encoding said therapeutic protein that is operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell, under conditions whereby the transgene encoding said therapeutic protein is expressed, and therapeutic benefit is produced in said airway epithelial cells.

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These and other aspects of the present invention are described in the Detailed Description of the Invention which follows directly.

Brief Description of the Drawings

5 FIGURE 1 depicts infection of NHBE cells by Ad 2.

FIGURE 2 depicts infection of NHBE cells by Ad 17.

10 FIGURE 3 plots the result of binding to human nasal polyp epithelial cell isolates by Ad 2 and Ad 17.

FIGURE 4 is a map of the vector Ad2/βgal-2/fiber Ad 17.

15 FIGURE 5 shows a comparison of the amino acid sequence of penton base from Ad 17 (top) [SEQ ID NO: 4] and Ad 2 (bottom) [SEQ ID NO: 5], and further depicts the variable RGD containing region.

FIGURE 6 depicts an amino acid sequence pileup for penton base from particular Ad serotypes, including f10 (from fowl) [SEQ ID NO: 6 through SEQ ID NO: 10].

15 FIGURE 7 shows a comparison of the amino acid sequence of fiber from Ad 17 (top) [SEQ ID NO: 11] and Ad 2 (bottom) [SEQ ID NO: 12].

20 FIGURE 8 depicts an amino acid sequence pileup for fiber from particular Ad serotypes [SEQ ID NO: 11 through SEQ ID NO: 22], including two forms of serotype 40 (40-1 and 40-2) which differ in that one variant has two (but non-identical) copies of the fiber gene.

FIGURE 9 shows the infection efficiency of colon cancer cell lines by adenovirus serotypes.

25 FIGURE 10 shows the infection efficiency of cancer cell lines by adenovirus serotypes.

Provided in the Sequence Listing attached hereto are also:

SEQ ID NO: 1, the complete nucleotide sequence of Ad 17;

SEQ ID NO: 2, the complete encoding nucleotide sequence for Ad 17 fiber;

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SEQ ID NO: 3, the complete encoding nucleotide sequence for Ad 17 penton base.

Detailed Description of the Invention

5 The present invention provides for chimeric adenoviral vectors comprising nucleotide sequence of a first adenovirus, wherein at least one gene of said first adenovirus encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by the corresponding gene from a second adenovirus belonging to subgroup D, said vectors
10 further comprising a transgene operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell. In a representative aspect thereof, the replaced encoding sequence correspond to the gene encoding the Ad fiber, hexon or penton base proteins, or combinations thereof.

In a further preferred embodiment of the invention, there are provided chimeric
15 adenoviral vectors comprising nucleotide sequence of a first adenovirus, wherein a portion of a gene thereof encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by a portion of the corresponding gene from a second adenovirus belonging to subgroup D, said vectors further comprising a transgene operably linked to a eucaryotic promoter to
20 allow for expression therefrom in a mammalian cell. In a representative aspect thereof, the replaced encoding sequence codes for a portion of the Ad fiber, hexon or penton base proteins, or combinations thereof. Where a portion of a gene from a second adenovirus is used to construct a chimeric adenoviral vector, such sequence will have a length sufficient to confer a desired serotypic-specific virus-cell interaction to the
25 vector.

The present invention involves the recognition that adenoviral vectors that are either based substantially upon the genome of Ad serotypes classified in subgroup D, or that contain certain Ad-protein encoding polynucleotide sequences of subgroup D adenovirus, are particularly effective at binding to, and internalizing within, human

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cells, such that therapeutic transgenes included in the adenoviral vector are efficiently expressed. This discovery is particularly surprising given that adenovirus serotypes of subgroup D are not clinically associated with human respiratory disease, and that, for example association with conjunctivitis is more typical. The recognition of this tropism is of particular relevance for the treatment by gene therapy of recognized disease states such as cystic fibrosis or α 1-antitrypsin deficiency. This discovery is particularly surprising given that adenovirus serotypes of subgroup D are not clinically associated with human respiratory disease, and that, for example association with conjunctivitis is more typical. The recognition of this tropism is of particular relevance for the treatment by gene therapy of recognized disease states such as cystic fibrosis or α 1-antitrypsin deficiency.

In a representative aspect of the invention, the adenoviral vectors further comprise nucleotide sequences coding for one or more transgenes and have enhanced tropism for airway epithelial cells. Preferably, the chimeric adenoviral vectors are replication-defective, a feature which contributes to the enhanced safety of adenoviral vectors administered to individuals.

Preferably, the second adenovirus is a member of subgroup D, and the replaced nucleotide sequence encodes a polypeptide selected from the group consisting of Ad fiber, a fragment of Ad fiber, Ad hexon, a fragment of Ad hexon, Ad penton base, and a fragment of Ad penton base. In a preferred embodiment, said second adenovirus is selected from the group consisting of serotypes Ad 9, Ad 15, Ad 17, Ad 19, Ad 20, Ad 22, Ad 26, Ad 27, Ad 28, Ad 30, and Ad 39. In a most preferred embodiment, the second adenovirus is Ad 17. In other preferred embodiments of the chimeric adenoviral vectors, the first adenovirus is selected from the group consisting of Ad 2, Ad 5, and Ad 12.

There is substantial evidence that any reported transforming properties of the E4 region of certain subgroup D serotypes do not extend to Ad serotypes whose use is preferred according to the practice of the present invention (see, for example, R. Javier

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et al., Science, 257, 1992, pp. 1267-1271). It is expected also that, for example, individual ORFs of subgroup D E4 region, such as ORF1, could be deleted.

Additional aspects of the invention include methods to provide biologically active and/or therapeutic proteins to mammalian cells, including, but not limited to,
5 the airway epithelial cells of individuals, in order to provide phenotypic benefit. According to this aspect of the invention, chimeric adenoviral vectors are used in which a nucleotide sequence of a first adenovirus is replaced by the corresponding nucleotide sequence of a second adenovirus. Preferably, the second adenovirus is a member of subgroup D, and the replaced nucleotide sequence encodes a polypeptide
10 encoding all or part of Ad fiber, Ad hexon, or Ad penton base, or combinations thereof.

A still further representative aspect of the invention involves providing a biologically active and/or therapeutic protein in the airway epithelial cells of a patient by administering to said cells an adenoviral vector comprising elements of an Ad 17 genome, and a transgene encoding said protein that is operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell, under conditions whereby the transgene encoding said protein is expressed, and the desired phenotypic benefit is produced in said airway epithelial cells. According to the practice of the invention, it is preferred that an chimeric adenovirus vector utilized to deliver a
15 transgene to the respiratory epithelium (including that of the nasal airway, trachea, and bronchi and alveoli of the lung), or to other tissues of the body, comprise serotypes within subgroup D, as such classification is recognized in the art.

In order to construct the chimeric adenoviral vectors of the invention, reference may be made to the substantial body of literature on how such vectors may be
20 designed, constructed and propagated using techniques from molecular biology and microbiology that are well-known to the skilled artisan. Specific examples of adenoviral vector genomes which can be used as the backbone for a chimeric adenoviral vector of the invention include, for example, Ad2/CFTR-1 and Ad2/CFTR-
2 and others described in U. S. Patent No. 5,670,488, issued September 23, 1997

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(incorporated herein by reference). Such vectors may include deletion of the E1 region, partial or complete deletion of the E4 region, and deletions within, for example, the E2 and E3 regions. Within the scope of the invention are, for example, 5 chimeric vectors which contain an Ad 2 backbone with one or more Ad 17 capsid proteins or fragments thereof in the virus. Other adenoviral vector genomic designs which can be used in the chimeric adenoviral vectors of the invention include those derived from allowed U.S. Patent Application Serial No. 08/409,874, filed March 24, 1995, and allowed U.S. Patent Application Serial No. 08/540,077, filed October 6, 1995 (both incorporated herein by reference).

10 To construct the recombinant chimeric adenoviral vectors of the invention which contain a transcription unit, the skilled artisan can use the standard techniques of molecular biology to engineer a transgene or a capsid protein into a backbone vector genome (Berkner, K.L., Curr. Top. Micro. Immunol. 158:39-66, 1992). For example, a plasmid containing a transgene and any operably linked regulatory 15 elements inserted into an adenovirus genomic fragment can be co-transfected with a linearized viral genome derived from an adenoviral vector of interest into a recipient cell under conditions whereby homologous recombination occurs between the genomic fragment and the virus. Preferably, a transgene is engineered into the site of an E1 deletion. As a result, the transgene is inserted into the adenoviral genome at the 20 site in which it was cloned into the plasmid, creating a recombinant adenoviral vector. The chimeric adenoviral vectors can also be constructed using standard ligation 25 techniques, for example, removing a restriction fragment containing a fiber gene from a first adenovirus and ligating into that site a restriction fragment containing a fiber gene from a second adenovirus. A representative example of a chimeric adenoviral vector of the invention is Ad2/βgal-2 fiber 17 (exemplified in Example 6).

Construction of the chimeric adenoviral vectors can be based on adenovirus DNA sequence information widely available in the field, e.g., nucleic acid sequence databases such as GenBank.

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Preparation of replication-defective chimeric adenoviral vector stocks can be accomplished using cell lines that complement viral genes deleted from the vector, e.g., 293 or A549 cells containing the deleted adenovirus E1 genomic sequences. The use of HER3 cells (human embryonic retinoblasts transformed by Ad 12), as a complementing cell line is of note. After amplification of plaques in suitable complementing cell lines, the viruses can be recovered by freeze-thawing and subsequently purified using cesium chloride centrifugation. Alternatively, virus purification can be performed using chromatographic techniques, e.g., as set forth in International Application No. PCT/US96/13872, filed August 30, 1996, incorporated herein by reference.

Titers of replication-defective chimeric adenoviral vector stocks can be determined by plaque formation in a complementing cell line, e.g., 293 cells. End-point dilution using an antibody to the adenoviral hexon protein may be used to quantitate virus production or infection efficiency of target cells (Armentano et al., 15 Hum. Gene Ther. 6:1343-1353, 1995, incorporated herein by reference).

Transgenes which can be delivered and expressed from a chimeric adenoviral vector of the invention include, but are not limited to, those encoding enzymes, blood derivatives, hormones, lymphokines such as the interleukins and interferons, coagulants, growth factors, neurotransmitters, tumor suppressors, apolipoproteins, 20 antigens, and antibodies, and other biologically active proteins. Specific transgenes which may be encoded by the chimeric adenoviral vectors of the invention include, but are not limited to, cystic fibrosis transmembrane regulator (CFTR), dystrophin, glucocerebrosidase, tumor necrosis factor, p53, p21, herpes simplex thymidine kinase and gancyclovir, retinoblastoma (Rb), and adenosine deaminase (ADA). Transgenes 25 encoding antisense molecules or ribozymes are also within the scope of the invention. The vectors may contain one or more transgenes under the control of one or more regulatory elements.

In addition to containing the DNA sequences encoding one or more transgenes, the chimeric adenoviral vectors of the invention may contain any

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expression control sequences such as a promoter or enhancer, a polyadenylation element, and any other regulatory elements that may be used to modulate or increase expression, all of which are operably linked in order to allow expression of the transgene. The use of any expression control sequences, or regulatory elements, 5 which facilitate expression of the transgene is within the scope of the invention. Such sequences or elements may be capable of generating tissue-specific expression or be susceptible to induction by exogenous agents or stimuli.

Infection of target cell by the chimeric adenoviral vectors of the invention may also be facilitated by the use of cationic molecules, such as cationic lipids as disclosed 10 in PCT Publication No. WO96/18372, published June 20, 1996, incorporated herein by reference.

Cationic amphiphiles have a chemical structure which encompasses both polar and non-polar domains so that the molecule can simultaneously facilitate entry across a lipid membrane with its non-polar domain while its cationic polar domain attaches 15 to a biologically useful molecule to be transported across the membrane.

Cationic amphiphiles which may be used to form complexes with the chimeric adenoviral vectors of the invention include, but are not limited to, cationic lipids, such as DOTMA (Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, 1987) (N-[1-(2,3-dioletloxy)propyl]-N,N,N - trimethylammonium chloride); DOGS 20 (dioctadecylamidoglycylspermine) (Behr et al., Proc. Natl. Acad. Sci. USA 86:6982-6986, 1989); DMRIE (1,2-dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide) (Felgner et al., J. Biol. Chem. 269:2550-2561, 1994; and DC-chol (3B [N-N', N'-dimethylaminoethane] -carbamoyl] cholesterol) (U.S. Patent No. 5, 283,185 to Epand et al.). The use of other cationic amphiphiles recognized in the art or which 25 come to be discovered is within the scope of the invention.

In preferred embodiments of the invention, the cationic amphiphiles useful to complex with and facilitate transfer of the vectors of the invention are those lipids which are described in PCT Publication No. WO96/18372, published June 20, 1996, which is incorporated herein by reference. Preferred cationic amphiphiles described

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herein to be used in the delivery of the plasmids and/or viruses are GL-53, GL-67, GL-75, GL-87, GL-89, and GL-120, including protonated, partially protonated, and deprotonated forms thereof. Further embodiments include the use of non-T-shaped amphiphiles as described on pp. 22-23 of the aforementioned PCT application, 5 including protonated, partially protonated and deprotonated forms thereof. Most preferably, the cationic amphiphile which can be used to deliver the vectors of the invention is spermine cholesterol carbamate (GL-67).

In the formulation of compositions comprising the chimeric adenoviral vectors of the invention, one or more cationic amphiphiles may be formulated with neutral co-lipids such as dileoylphosphatidylethanolamine (DOPE) to facilitate delivery of the vectors into a cell. Other co-lipids which may be used in these complexes include, but are not limited to, diphytanoylphosphatidylethanolamine, lyso-phosphatidylethanolamines, other phosphatidylethanolamines, phosphatidylcholines, 10 lyso-phosphatidylcholines and cholesterol. A preferred molar ratio of cationic amphiphile to colipid is 1:1. However, it is within the scope of the invention to vary 15 this ratio, including also over a considerable range. In a preferred embodiment of the invention, the cationic amphiphile GL-67 and the neutral co-lipid DOPE are combined in a 1:2 molar ratio, respectively, before complexing with a chimeric adenoviral vector for delivery to a cell.

20 In the formulation of complexes containing a cationic amphiphile with a chimeric adenoviral vector, a preferred range of 10^7 - 10^{10} infectious units of virus may be combined with a range of 10^4 - 10^6 cationic amphiphile molecules/viral particle.

The infection efficiency of the chimeric adenoviral vectors of the invention 25 may be assayed by standard techniques to determine the infection of target cells. Such methods include, but are not limited to, plaque formation, end-point dilution using, for example, an antibody to the adenoviral hexon protein, and cell binding assays using radiolabelled virus. Improved infection efficiency may be characterized as an increase in infection of at least an order of magnitude with reference to a control virus. Where

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a chimeric adenoviral vector encodes a marker or other transgene, relevant molecular assays to determine expression include the measurement of transgene mRNA, by, for example, Northern blot, S1 analysis or reverse transcription-polymerase chain reaction (RT-PCR). The presence of a protein encoded by a transgene may be detected by 5 Western blot, immunoprecipitation, immunocytochemistry, or other techniques known to those skilled in the art. Marker-specific assays can also be used, such as X-gal staining of cells infected with a chimeric adenoviral vector encoding β -galactosidase.

In order to determine transgene expression and infection efficiency *in vivo* using the constructs and compositions of the invention, animal models may be 10 particularly relevant in order to assess transgene persistence against a background of potential host immune response. Such a model may be chosen with reference to such parameters as ease of delivery, identity of transgene, relevant molecular assays, and assessment of clinical status. Where the transgene encodes a protein whose lack is associated with a particular disease state, an animal model which is representative of 15 the disease state may optimally be used in order to assess a specific phenotypic result and clinical improvement. However, it is also possible that particular chimeric adenoviral vectors of the invention display enhanced infection efficiency only in human model systems, e.g., using primary cell cultures, tissue explants, or permanent cell lines. In such circumstances where there is no animal model system available in 20 which to model the infection efficiency of a chimeric adenoviral vector with respect to human cells, reference to art-recognized human cell culture models will be most relevant and definitive.

Relevant animals in which the chimeric adenoviral vectors may be assayed include, but are not limited to, mice, rats, monkeys, and rabbits. Suitable mouse 25 strains in which the vectors may be tested include, but are not limited to, C3H, C57Bl/6 (wild-type and nude) and Balb/c (available from Taconic Farms, Germantown, New York).

Where it is desirable to assess the host immune response to vector administration, testing in immune-competent and immune-deficient animals may be

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compared in order to define specific adverse responses generated by the immune system. The use of immune-deficient animals, e.g., nude mice, may be used to characterize vector performance and persistence of transgene expression, independent of an acquired host response.

- 5 In a particular embodiment where the transgene is the gene encoding cystic fibrosis transmembrane regulator protein (CFTR) which is administered to the respiratory epithelium of test animals, expression of CFTR may be assayed in the lungs of relevant animal models, for example, C57Bl/6 or Balb/c mice, cotton rats, or Rhesus monkeys. Molecular markers which may be used to determine expression
- 10 include the measurement of CFTR mRNA, by, for example, Northern blot, S1 analysis or RT-PCR. The presence of the CFTR protein may be detected by Western blot, immunoprecipitation, immunocytochemistry, or other techniques known to those skilled in the art. Such assays may also be used in tissue culture where cells deficient in a functional CFTR protein and into which the chimeric adenoviral vectors have
- 15 been introduced may be assessed to determine the presence of functional chloride ion channels - indicative of the presence of a functional CFTR molecule.

The chimeric adenoviral vectors of the invention have a number of in vivo and in vitro utilities. The vectors can be used to transfer a normal copy of a transgene encoding a biologically active protein to target cells in order to remedy a deficient or dysfunctional protein. The vectors can be used to transfer marked transgenes (e.g., containing nucleotide alterations) which allow for distinguishing expression levels of a transduced gene from the levels of an endogenous gene. The chimeric adenoviral vectors can also be used to define the mechanism of specific viral protein-cellular protein interactions that are mediated by specific virus surface protein sequences. The vectors can also be used to optimize infection efficiency of specific target cells by adenoviral vectors, for example, using a chimeric adenoviral vector containing Ad 17 fiber protein to infect human nasal polyp cells. Where it is desirable to use an adenoviral vector for gene transfer to cancer cells in an individual, a chimeric adenoviral vector can be chosen which selectively infects the specific type of target

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cancer cell and avoids promiscuous infection. Where primary cells are isolated from a tumor in an individual requiring gene transfer, the cells may be tested against a panel of chimeric adenoviral vectors to select a vector with optimal infection efficiency for gene delivery. The vectors can further be used to transfer tumor antigens to dendritic 5 cells which can then be delivered to an individual to elicit an anti-tumor immune response. Chimeric adenoviral vectors can also be used to evade undesirable immune responses to particular adenovirus serotypes which compromise the gene transfer capability of adenoviral vectors.

The present invention is further directed to compositions containing the 10 chimeric adenoviral vectors of the invention which can be administered in an amount effective to deliver one or more desired transgenes to the cells of an individual in need of such molecules and cause expression of a transgene encoding a biologically active protein to achieve a specific phenotypic result. The cationic amphiphile-plasmid complexes or cationic amphiphile-virus complexes may be formulated into 15 compositions for administration to an individual in need of the delivery of the transgenes.

The compositions can include physiologically acceptable carriers, including any relevant solvents. As used herein, "physiologically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, 20 isotonic and absorption delaying agents, and the like. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the compositions is contemplated.

Routes of administration for the compositions containing the chimeric adenoviral vectors of the invention include conventional and physiologically acceptable routes such as direct delivery to a target organ or tissue, intranasal, 25 intravenous, intramuscular, subcutaneous, intradermal, oral and other parenteral routes of administration.

The invention is further directed to methods for using the compositions of the invention in vivo or ex vivo applications in which it is desirable to deliver one or more

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transgenes into cells such that the transgene produces a biologically active protein for a normal biological or phenotypic effect. In vivo applications involve the direct administration of one or more chimeric adenoviral vectors formulated into a composition to the cells of an individual. Ex vivo applications involve the transfer of 5 a composition containing the chimeric adenoviral vectors directly to autologous cells which are maintained in vitro, followed by readministration of the transduced cells to a recipient.

Dosage of the chimeric adenoviral vector to be administered to an individual for expression of a transgene encoding a biologically active protein and to achieve a 10 specific phenotypic result is determined with reference to various parameters, including the condition to be treated, the age, weight and clinical status of the individual, and the particular molecular defect requiring the provision of a biologically active protein. The dosage is preferably chosen so that administration causes a specific phenotypic result, as measured by molecular assays or clinical markers. For 15 example, determination of the infection efficiency of a chimeric adenoviral vector containing the CFTR transgene which is administered to an individual can be performed by molecular assays including the measurement of CFTR mRNA, by, for example, Northern blot, S1 or RT-PCR analysis or the measurement of the CFTR protein as detected by Western blot, immunoprecipitation, immunocytochemistry, or 20 other techniques known to those skilled in the art. Relevant clinical studies which could be used to assess phenotypic results from delivery of the CFTR transgene include PFT assessment of lung function and radiological evaluation of the lung. Demonstration of the delivery of a transgene encoding CFTR can also be 25 demonstrated by detecting the presence of a functional chloride channel in cells of an individual with cystic fibrosis to whom the vector containing the transgene has been administered (Zabner et al., J. Clin. Invest. 97:1504-1511, 1996). Transgene expression in other disease states can be assayed analogously, using the specific clinical parameters most relevant to the condition.

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Dosages of a chimeric adenoviral vector which are effective to provide expression of a transgene encoding a biologically active protein and achieve a specific phenotypic result range from approximately 10^8 infectious units (I.U.) to 10^{11} I.U. for humans.

5 It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated, each unit containing a predetermined quantity of active ingredient calculated to produce the specific phenotypic effect in association with the required 10 physiologically acceptable carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly depend on the unique characteristics of the chimeric adenoviral vector and the limitations inherent in the art of compounding. The principal active ingredient (the chimeric adenoviral vector) is compounded for convenient and effective administration in effective amounts with the physiologically 15 acceptable carrier in dosage unit form as discussed above.

Maximum benefit and achievement of a specific phenotypic result from administration of the chimeric adenoviral vectors of the invention may require repeated administration. Such repeated administration may involve the use of the same chimeric adenoviral vector, or, alternatively, may involve the use of different 20 chimeric adenoviral vectors which are rotated in order to alter viral antigen expression and decrease host immune response.

The practice of the invention employs, unless otherwise indicated, conventional techniques of protein chemistry, molecular virology, microbiology, recombinant DNA technology, and pharmacology, which are within the skill of the 25 art. Such techniques are explained fully in the literature. See, e.g., Current Protocols in Molecular Biology, Ausubel et al., eds., John Wiley & Sons, Inc., New York, 1995, and Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Co., Easton, PA, 1985.

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The invention is further illustrated by the following specific examples which are not intended in any way to limit the scope of the invention.

Examples

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Example 1 Infection of NHBE cells by adenovirus serotypes of subgroup D

Normal human bronchial epithelial ("NHBE") cells were obtained from Clonetics (San Diego, CA), and plated on Costar (Cambridge, MA) Transwell-Clear polyester membranes that were pre-coated with human placental collagen. The wells 10 were placed in a cluster plate and cells were fed every day for one week by changing the medium in both the well and the plate. After one week the media was removed from the wells to create an air-liquid interface, and the cells were then fed only by changing the medium in the cluster plate, every other day for one week. Cells were infected at an moi of 1 by adding virus (see below) to the transwell, followed by an 15 incubation time of 1.5-2 hours. At the end of the incubation period, the medium was removed and the cells were gently rinsed with fresh medium. Thirty-six hours post-infection the cells were fixed with 1:1 acetone:methanol, permeabilized with a solution of 0.05% Tween 20 in PBS, and stained with FITC labeled anti-hexon antibody (Chemicon, Temecula, CA) to visualize cells that had been productively infected (i.e. 20 to visualize virus replication). Cells were also subjected to the DAPI staining procedure in order to visualize the total number of nuclei. The results could be readily determined upon simple inspection.

Wild type Ad serotypes within subgroup D that were tested included 9, 15, 17, 19, 20, 22, 26, 27, 28, 30, and 39 (all from the American Type Culture Collection, 25 Rockville, MD). An Ad 2 (obtained as DNA from BRL, Gaithersburg, MD, and used to transfect 293 cells in order to generate virus stock) was used as a control. Infection observed with all of the subgroup D serotypes was superior to that observed with Ad 2, with the best results being achieved with Ad 9, Ad 17, Ad 20, Ad 22, and Ad 30.

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Additionally, it was determined that each of the above-mentioned serotypes of subgroup D was more effective in the NHBE cell assay under similar circumstances than any other serotype tested than belongs to a subgroup other than D. In this regard, the following serotypes were also tested: 31(subgroup A); 3(subgroup B); 7(subgroup B); 7a(subgroup B); 14(subgroup B); 4(subgroup E); and 41(subgroup F). In a further 5 experiment, serotype 35 (subgroup A) may have performed as well as the least effective members of subgroup D that were tested.

Example 2 Infection of clinical isolate bronchial epithelial cells

Following generally the procedures of Example 1, human bronchial epithelial 10 cells recovered from healthy human volunteers were infected with either Ad 2 (as above, Ad 2 DNA was obtained from BRL, and this DNA was used to transfect 293 cells to generate virus) (Figure 1), or Ad 17 (from ATCC) (Figure 2), all at an moi of 50. Cells were left in contact with virus for 30 minutes, 3 hours, or 12 hours.

The increased tropism of Ad 17 for human bronchial epithelial cells, compared 15 with Ad 2, is readily apparent upon inspection of Figures 1 and 2. In the Figures, the right hand columns (panels D, E, and F, stained in blue) show total numbers of cells present (from DAPI staining as above), whereas the left hand columns (panels A, B, and C, stained in green) quantify adenovirus hexon protein present in the infected cells 20 (from FITC-labeled anti-hexon antibody, as above). Panels A and D result from 30 minute incubation times, panels B and E result from 3 hour incubation times, and panels C and F result from 12 hour incubation times. As measured by the technique employed, infection of airway epithelia by Ad 17 is at least 50 fold greater than by Ad 2 for the thirty minute incubation time.

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Example 3 Binding of Ad 2 and Ad 17 to human nasal polyp cell isolates

293 cells, a complementing cell line developed by Graham et al. (see Gen. Virol. , 36, 1977, pp. 59-72), were infected with either wild type Ad 2 or wild type Ad 17. Five hours post-infection the media was removed and replaced with methionine

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free media containing S^{35} metabolic label (Amersham). After an additional six hours, fresh media was added and the labeling was allowed to proceed for a total of 18 hours, after which the S^{35} media was removed and replaced with fresh media. Thirty hours post-infection the cells were harvested and lysed and the labeled Ad 2 or Ad 17 viruses were purified by CsCl gradient centrifugation. The recovered viruses were then used in an assay to determine their relative binding efficiency on human nasal polyp cells.

In order to perform the assay, ciliated human airway epithelial cells were recovered from nasal polyps of healthy volunteers. The results from two such isolates, NP-14 and NP-15, are reported here (see Figure 3). Radiolabeled virus was then incubated with the isolated cells in wells for specified times (5 or 30 minutes, see Figure 3). The cells were then rinsed and measured for radioactivity. Binding as reported in Figure 3 indicates the percent of input radioactivity that is cell associated. It was determined that for both cell isolate populations, using either 5 or 30 minute incubations, cell associated radioactivity was 10-fold enhanced if Ad 17 rather than Ad 2 was used.

Example 4 Fiber competition

A549 cells (a human lung carcinoma line, obtained from the American Type Culture Collection as ATCC CCL-185) were plated at 3×10^4 cells per well in 96-well dishes. Since the number of receptor sites for adenovirus fiber on the cell surface has been estimated to be approximately 10^5 receptors per cell, the receptors in the plated cells were saturated, in this example, with $0.1\mu g$ of purified full length Ad 2 fiber protein (obtained from Paul Freimuth, Brookhaven National Laboratory, Upton, NY), which corresponds to approximately 100 molecules of fiber per receptor. Cells were incubated with Ad 2 fiber in PBS for two hours at $37^\circ C$.

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The cells were subsequently infected at an moi of 1 (using either Ad 2 provided as above, or wild type Ad 17) for one hour, after which the cells were rinsed, and fresh medium was added. Control cultures were incubated with PBS with no added protein for two hours and then subsequently infected as described above. Forty 5 hours post-infection the cells were fixed with 1:1 acetone:methanol, permeabilized with 0.05% Tween 20 in PBS and stained with FITC labeled anti- Ad 2 hexon antibody, as described in Example 1. As determined by this assay, the number of cells infected (stained) with Ad 2 was reduced by approximately 90% in cultures that were pre-incubated with Ad 2 fiber as compared to control cultures. However, no effect on 10 Ad 17 infection was observed by the pre-incubation of A549 cells with full length Ad 2 fiber.

Example 5 Use of Ad 2 fiber knob in a binding competition
experiment with Ad 2

15 Further competition experiments were performed with Ad 2 and Ad 17 fiber knobs that had been expressed and purified from E. coli. DNA sequences encoding both protein fragments were designed so that the fiber knobs expressed therefrom would contain histidine tags in order to permit nickel- column purification. The yield 20 of soluble fiber knob trimer, purified by the Ni-NTA method (Qiagen, Chatsworth, CA), was ~25 μ g/50ml culture. A significant portion of the total knob protein expressed appeared to remain in a monomeric (and insoluble) form. The soluble trimeric material obtained was used for a preliminary competition experiment. Wild type Ad 2 and Ad 17 were used to infect A549 cells, or cells that had been pre- 25 incubated with excess (about 100 molecules of trimer per receptor) Ad 2 fiber knob or Ad 17 fiber knob. The results indicated that Ad 2 fiber knob, but not Ad 17 knob, could block Ad 2 infection. Additionally, Ad 17 infection was not blocked by E. coli-expressed fiber knobs of either serotype, suggesting that the mechanism of Ad 2 and Ad 17 infections is different.

Example 6 Construction of the chimeric vector Ad2/βgal-2/fiber Ad 17

The vector Ad2/βgal-2 was constructed as follows. A CMV β gal expression cassette was constructed in a pBR322-based plasmid that contained Ad 2 nucleotides 1-10,680 from which nucleotides 357-3328 were deleted. The deleted sequences were replaced with (reading from 5' to 3'): a cytomegalovirus immediate early promoter (obtained from pRC/CMV, Invitrogen), lacZ gene encoding β -galactosidase with a nuclear localization signal, and an SV40 polyadenylation signal (nucleotides 2533-10 2729). The resulting plasmid was used to generate Ad2/βgal-2 by recombination with Ad2E4ORF6 (D. Armentano et al., Human Gene Therapy , 6, 1995, pp 1343 -1353).

A chimeric Ad2/βgal-2/fiber Ad 17 viral vector (Figure 4) was then contructed as follows. pAdORF6 (D. Armentano et al., Human Gene Therapy , 6, 1995, pp 1343 -1353 was cut with Nde and BamHI to remove Ad 2 fiber coding and polyadenylation 15 signal sequences (nucleotides 20624-32815). An NdeI-BamHI fragment containing Ad 17 fiber coding sequence (nucleotides 30984-32095) was generated by PCR and ligated along with an SV40 polyadenylation signal into NdeI-BamHI cut pAdORF6 to generate pAdORF6fiber17. This plasmid was cut with PacI and then ligated to PacI-cut Ad2/βgal-2 DNA to generate Ad2/βgal-2fiber 17. Any desired transgene may be 20 substituted in this construct for the reporter gene.

A similar construct can be prepared using a DNA sequence that encodes Ad 17 penton base instead of Ad 17 fiber. Alternatively, only a subregion of the penton base of Ad 2 need be subject to replacement, such as by inserting into the vector a nucleotide encoding sequence corresponding to any amino acid subsequence of Ad 17 25 penton base amino acids 283-348 (see the marked sequence in Figure 5A) in replacement for any subsequence of Ad 2 penton base amino acids 290-403. Preferably, the replaced sequence of Ad 2 and the inserted sequence of Ad 17 includes the RGD domain of each. Use of nucleotide sequence corresponding to penton base amino acid sequence for other subgroup D serotypes is also within the

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practice of the invention. It is also within the scope of the invention to replace a subregion of the fiber protein in the Ad 2 vector with a subregion from another adenovirus serotype, for example, Ad 17.

- 5 Example 7 Ad2/βgal-2f17 shows increased infection efficiency on human airway explants

Both human and monkey trachea explants, about 1 cm², were placed on top of an agar support. Each explant was infected at an moi of 200 of either Ad2/βgal-2 or Ad2/βgal-2f17 assuming a cell density of 1 x 10⁶ per cm² of explant. Explants were exposed to virus for three hours and were then rinsed with NHBE media. Two days post-infection explants were stained with X-gal and infection efficiency was assessed. On the monkey explants Ad2/βgal-2 gave rise to a higher infection efficiency than Ad2/βgal-2f17. Patches of stained cells were detected in explants exposed to Ad2/βgal-2 but very few cells stained in explants exposed to Ad2/βgal-2f17. A different result was obtained on human trachea explants. On these explants Ad2/βgal-2f17 infection gave rise to a much higher infection efficiency than Ad2/βgal-2 infection. Approximately 5-10% of the cells in explants exposed to Ad2/βgal-2f17 stained with X-gal whereas very few cells were stained in explants exposed to Ad2/βgal-2. No background staining was observed in either monkey or human explants that were not exposed to virus.

The results indicate that the exchange of Ad 2 fiber for Ad 17 fiber in Ad2/βgal-2f17 was sufficient to significantly increase infection efficiency of human tracheal airway cells by an adenovirus type 2 based vector.

- 25 Example 8 Adenovirus subgroup screening on human cancer cell lines

Identification of adenovirus subgroup that best infects a particular tumor type may be useful in designing vectors to optimally target cancer cells *in vivo*. In order to determine the adenovirus subgroup that best infects a particular type of cancer cell, cancer cells were seeded into a 96 well plate and infected with and moi of 5. Infection

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efficiency was determined by staining of infected cells using an anti-hexon antibody. The adenovirus subgroups were represented by the following serotypes: A: Ad 31; B: Ad 3; C: Ad 2; D: Ad 17; E: Ad 4; and F: Ad 41.

Subgroup D (Ad 17) has a significantly higher infection rate of the colon
5 cancer cell line CaCo-2 than other cell types, with an infection rate of 70%, while Ad
2 only infected 20% of the cells (Figure 9).

Subgroup D (Ad 17) was effective in infecting ovarian cancer cell line SK-
OV3. Infection was measured at 90% (Figure 10).

10 Sequence Listing

Included herewith on the following pages are informal copies of SEQ ID NO:
1 through SEQ ID NO: 3.

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1 CATCATCAAT AATATACCCC ACAAAAGTAAA CAAAAGTTAA TATGCAAATG AGGTTTTAAA
 61 TTAGGGCGG GGCTACTGCT GATTGGCGA GAAACGTTGA TGCAAATGAC GTACGACGC
 121 ACGGCTAACG GTGCCGCGG AGCGGTGGCC TAGCCCGAA GCAAGTCGGG GGGCTGATGA
 181 CGTATAAAAA AGCGGACTTT AAACCCGGAA ACGGCCGATT TTCCCGGGC CACGCCCGGA
 241 TATGAGGTAA TTCTGGCGG ATGCAAGTGA AATTAGGTCA TTTTGGCGG AAAACTGAAT
 301 GAGGAAGTGA AAAGTAAAA ATACCGGTCC CGCCCAGGGC GGAATATTTA CCGAGGGCCG
 361 AGAGACTTTG ACCGATTACG TGTGGGTTTC GATTGGGTG TTTTTTCGCG AATTCGGCG
 421 TCCGTCTAA AGTCCGGTGT TTATGTCACA GATCAGCTGA TCCACAGGGT ATTTAAACCA
 481 GTCGAGCCCG TCAAGAGGCC ACTCTTGAGT GCCAGCGAGT AGAGATTCT CTGAGCTCG
 541 CTCCAGAGT GTGAGAAAAA TGAGACACCT GCGCCTCCG CCTGAACTG TGCCCTTGA
 601 CATGGCCGCA TTATTGCTGG ATGACTTTGT GAGTACAGTA TTGGAGGATG AACTGCAACC
 661 AACTCCGTC GAGCTGGAC CCACACTTC GAGACCTCTAT GATTGGAGG TAGATGCCA
 721 GGAGGACGAC CCGAACGAAG ATGCTGTGAA TTTAATATTT CCAGAATCTC TGATTCTCA
 781 GGCTGACATA GCCAGCGAAG CTCTACCTAC TCCACTTCAT ACTCCAACTC TGTCACCCAT
 841 ACCTGAATTG GAAGAGGAGG ACGAGTTAGA CCTCCGGTGT TATGAGGAAG GTTTTCTCC
 901 CAGCGATTCA GAGGACGAAC AGGGTGACCA GAGCATGGCT CTAATCTAG ACTATGCTTG
 961 TGTGGTTGTG GAAGAGCATT TTGTGTGGA CAATCCTGAG GTGCCCGGGC AAGGCTGTAA
 1021 ATCCTGCCAG TACCACCGGG ATAAGACCGG AGACAGGAAC GCCTCTGTG CTCTGTGTTA
 1081 CATGAAAAAG AACTTCAGCT TTATTTACAG TAAGTGGAGT GAATGTGAGA GAGGCTGAGT
 1141 CCTTAAGACA TAACCTGGTG ATGCTTCAC ACAGCTGTCTA AGTGTGGTTT ATTTTGTTC
 1201 TAGTCCGGT GTCAGAGGAT GGTCTACACC CTCAGAAGAA GACCACCCGT GTCCCCCTGA
 1261 TCTGTCAAGC GAAACGCCCG TGCAAGTGCA CAGACCCACC CCAGTCAGAC CCAGTGGCGA
 1321 GAGGCAGGCA GCTGTTGAAA AAATTGAGGA CTTGTTACAT GACATGGTG GGGATGAACC
 1381 TTTGGACCTG AGCTGAAAC GTCCCAGGAA ACTAGGGCAGA GCTGCGCTTA GTCATGTGTA
 1441 AATAAAAGTTG TACAATAAAA ATTATATGTG ACGCATGCAA GGTGTGGTTT ATGACTCATG
 1501 GGCGGGGCTT AGTTCTATAT AAGTGGCAAC ACCTGGGCAC TGGAGCACAG ACCTTCAGGG
 1561 AGTTCTGAT GGATGTGTCG ACTATCCTTC CAGACTTTAG CAAGACACGC CGGCTTGAG
 1621 AGGATAGTTC AGACGGGTGC TCCGGGTTCT GGAGACACTG GTTGGAACT CCTCTATCTC
 1681 GCCTGGTGTG CACAGTTAAA AAGGATTATA ACGAGGAATT TGAAAATCTT TTTGCTGATT
 1741 GCTCTGCCCT GCTAGATTCT CTGAATCTCG GCCACCGTC CCTTTTCCAG GAAAGGGTAC
 1801 TCCACAGCCT TGATTTTCC AGCCCAGGGC GCACTACAGC CGGGGTGCT TTTGTTGGTTT
 1861 TTCTGGTTGA CAAATGGAGC CAGAACACCC AACTGAGCAG GGGCTACATT CTGGACTTCG
 1921 CAGCCATGCA CCTGTGGAGG GCATGGGTCA GGCAGGGGG ACAGAGAATC TTGAACACT
 1981 GGCTCTACA GCCAGCAGCT CCGGGTCTC TTGCTCTACA CAGACAAACA TCCATGTGTTG
 2041 AGGAAGAAAT GAGGCAGGCC ATGGACGAGA ACCCGAGGAG CGGCTCTGGAC CCTCCGTGG
 2101 AAGAGGAGTT GGATTGAATC AGGTATCCAG CCTGTACCCA GAGCTTAGCA AGGTGCTGAC
 2161 ATCCATGGCC AGGGGAGTGA AGAGGGAGAG GAGCGATGGG GGCATACCC GGATGATGAC
 2221 CGAGCTGACG GCCAGTCTGA TGAATGCAAA GCGCCAGAG CGCCTTACCT GGTACGAGCT
 2281 ACAGCAGGAG TCCAGGGATG AGTTGGGCT GATGCAAGGAT AAATATGGCC TGGAGCAGAT
 2341 AAAAACCCAT TGTTGAAACC CAGATGAGGA TTGGGAGGAG GCTATTAAGA AGTATGCCA
 2401 GATAGCCCTG CGGCCAGATT GCAAGTACAT AGTGACCAAG ACCGTGAATA TCAGACATGC
 2461 TGCTACATCT CGGGGAACGG GGCAGAGGTG GTCATGATA CCTGGACAA GGCGCCTTT
 2521 AGGTGTTGCA TGATGGGAT GAGACGGGA GTGATGAATA TGAATTCCAT GATCTTTATG
 2581 AACATGAAGT TCAATGGAGA GAAAGTTAA TGGGGCTGTG TCATGGCCAA CAGCCACATG
 2641 ACCCTGCATG GCTGCGACTT TTTCGGCTTT AACAATATGT GCGCAGAGGT CTGGGGCGCT
 2701 TCCAAGATCA GGGGATGTAA TTTTATGGC TGCTGGATGG CGCTGGTCGG AAGACCCAAAG
 2761 AGCGAGATGT CTGTGAAGCA GTGTGTGTTT GAGAAATGCT ACCTGGGAGT CTCTACCGAG
 2821 GGCAATGCTA GAGTGAGGCA CTGCTCTTC CTGGAGACGG GCTGCTCTG CCTGGTGAAG
 2881 GGCACAGCCT CTCTGAAGCA TAATATGGT AAGGGCTGCA CGGATGAGGG CATGTACAAC
 2941 ATGCTGACTG CGACTGGGG GTCTGTCTA TCCGTGAAGAA CATCCATGTG ACCTCCCACC
 3001 CCAGAAAGAA GTGGCCAGTG TTTGAGAATA ACATGCTGAT CAAGTGCCAC ATGCACCTGG
 3061 GCGCCAGAAG GGGCACCTTC CAGCCGTAC AGTGCACCTT TAGCCAGACC AAGCTGCTGT
 3121 TGGAGAACGA TGCCCTCTCC AGGGTGAACC TGAACGGCAT CTTTGACATG GATGTCTCG
 3181 TGTACAAGAT CCTGAGATAC GATGAGACCA AGTCCAGGGT GCGCGCTTGC GAGTGGGGGG
 3241 GCAGACACAC CAGGATGCAAG CCAGTGGCCC TGGATGTGAC CGAGGAGCTG AGACCAAGACC
 3301 ACCTGGTGAT GGCCTGTACC GGGACGGAGT TCAGCTCCAG TGGGGAGGAC ACAGATTAGA
 3361 GGTAGGTTTG AGTAGTGGGC GTGGCTAAGG TGACTATAAA GGCGGGTGTGTC TTACGAGGGT

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3421 CTTTTGCTT TTCTGCAGAC ATCATGAACG GGACGGCGG GGCTTCGAA GGGGGCTTT
 3481 TTAGCCCTTA TTTGACAACC CGCCTGCCAG GATGGGCCGG AGTCGTCAG AATGTGATGG
 3541 GATCGACGGT GGACGGCGC CCAGTCTTC CAGCAAATTG CTCGACCATG ACCTACGCGA
 3601 CCGTGGGAA CTCGTCGCTT GACAGCACCG CCGCAGCCGC GGCAGCCGCA GCCGCCATGA
 3661 CAGCGACGG ACTGGCCTCG AGCTACATGC CCAGCAGCAG CAGTAGCCCC TCTGTGCCA
 3721 GTTCCATCAT CGCCGAGGAG AACTGCTGGC CCTGCTGGCC GAGCTGGAAG CCCTGAGCCG
 3781 CCAGCTGGCC GCCCTGACCC AGCAGGTGTC CGAGCTCCGC GAACAGCAGC AGCAAAATAA
 3841 ATGATTCAAT AAACACATAT TCTGATTCAA ACAGCAAAGC ATCTTTATTA TTTATTTTT
 3901 CGCGCGGGT AGGCCCTGGT CCACCTCTCC CGATCATTTGA GAGTGCCTGT GATTTTTCC
 3961 AAGACCCCCG AGAGGTGGG TTGGATGTTG AGGTACATGG GCATGAGCCC GTCCCAGGGG
 4021 TGGAGGTAGC ACCACTGCAT GCCCTCGTGC TCTGGGTCG TGTGTTAGAT GATCCAGTCA
 4081 TAGCAGGGGC GCTGGCGTG GTGCTGGATG ATGTCCTTGA GGAGGAGACT GATGGCACG
 4141 GGGAGCCCCCT TGGTGTAGGT GTTGGCAAAG CGGTTGAGCT GGGAGGGATG CATGCGGGGG
 4201 GAGATGATGT GCAGTCTGGC CTGGATCTTG AGGTTGGCAGA TGTTGCCACC CAGATCCCGC
 4261 CGGGGGTTCA TGTGTCGAG GACCACCAGG ACGGTGTTAGC CGTGCACATT GGGGAACCTTA
 4321 TCATGCAACT TGGAAAGGAA TGCGTGGAAAG AATTGAGA CGCCCTTGTG CCCGCCAGG
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 33421 GTTAATGCTG CCTTGCTAT CATTCAAGGG GGGCGGTGGC AGGATGGAA GAACCATTTT
 33481 TATTCCAAAC GGTCTCGAAG GACCGATAAAG TGCAAGTCA GCAGGTGACA GCGTTCCCC
 33541 CGCCTGTGCT GGTGGAAACA GACAGCCAGG TCAAAACCCA CTCTATTITC AAGGTGCTCG
 33601 ACCGTGGCTT CGAGCAGTGG CTCTACCGCT ACATCCAGCA TAAGAATCAC ATTAAAGGCT
 33661 GGGCCCTCCAT CGATTTCATC AATCATCAGG TTACATTCT GCACCATCCC CAGGTAATT
 33721 TCATTTTCC AGCCTTGGAT TATCTCTACA AATTGTTGGT GTAAATCCAC TCCGCACATG
 33781 TTGAAAAGCT CCCACAGTGC CCCCTCCACT TTCATAATCA GGCAGACCTT CATAATAGAA
 33841 ACAGATCCTG CTGCTCCACC ACCTGAGCG TGTTCAAAC ACAAGATTG AATAAGGTT
 33901 TGCCCTCCGC CCTGAGCTCG CGCCCTCAATG TCAGCTGCAA AAAGTCACTT AAGTCCTGG
 33961 CCACTACAGC TGACAATTCA GAGCCAGGG TAAGCGTGG ACTGGCAAGC GTGAGGGAAA
 34021 ACTTTAATGC TCCAAAGCTA GCACCCAAAA ACTGCATGCT GGAATAAGCT CTCTTTGTGT
 34081 CTCCGGTGAT GCCTTCCAAA ATGTGAGTGA TAAAGCGTGG TAGTTTTTC TTTAATCATT
 34141 TGCCTAATAG AAAAGTCCTG TAAATAAGTC ACTAGGACCC CAGGGACCAC AATGTGGTAG

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34201 CTTACACCGC GTCGCTGAAA GCATGGTTAG TAGAGATGAG AGTCTGAAAA ACAGAAAGCA
34261 TGGCCTAAAC TAAGGTGGCT ATTTCACTG AAGGAAAAAT CACTCTTCC AGCAGCAGGG
34321 TACCCACTGG GTGGCCCTTG CGGACATACA AAAATCGGTG CGTGTGATTA AAAAGCAGCA
34381 CAGTAAGTTC CTGTCTCTT CCGGCAAAAA TCACATGGA CTGGGTTAGT ATGTCCCTGG
34441 CATGGTAGTC ATTCAAGGCC ATAATCTGC CCTGATATCC AGTAGGAACC AGCACACTCA
34501 CTTTTAGGTG AAGCAATACC ACCCATGCG GAGGAATGTG GAAAGATTCA GGGCAAAAAA
34561 AATTATATCT ATTGCTAGCC CTTCTGGAC GGGACAAATC CTCCAGGACT ATCTATGAAA
34621 GCATACAGAG ATTCAAGCCAT AGCTCAGCCC GCTTACCAAGT AGACAAAGAG CACAGCAGTA
34681 CAAGCGCAA CAGCAGCGAC TGACTACCCA CTGACTTAGC TCCCTATTTA AAGGCACCTT
34741 ACACTGACGT AATGACCAAA GGTCTAAAAA CCCCAGCCAAA AAAACACACA CGCCCTGGGT
34801 GTTTTGCGA AAACACTTCC GCGTTCTCAC TTCTCGTAT CGATTTCTG ACTTGACTTC
34861 CGGGTTCCCA CGTTACGTCA CTTTGCCCT TACATGTAAC TTAGTCGTAG GGCGCCATCT
34921 TGCCCCACGTC CAAAATGGCT TACATGTCCA GTTACGCCCT CGCGGCGACC GTTAGCCGTG
34981 CGTCGTGACG TCATTGCTT CAACGTTCT CGGCCAATCA GCAGTAGCCC CGCCCTAAAT
35041 TTAAACCTC ATTTGCATAT TAACCTTTGT TTACTTTGTG GGGTATATTA TTGATGATG

ATGTCAAAGAGGCTCCGGGTGGAAGATGACTCAACCCCGTCTACCCCTA
TGGCTACGCGCGGAATCAGAATATCCCCTCCTCACTCCCCCTTGTCTC
CTCCGATGGATTCAAAAACCTCCCCCTGGGGTCTGTCACTCAAACGGC
TGACCCAATCACCATAGCCAATGGTGTCTCACTCAAGGTGGGAGGGG
GACTTACTTGCAAGAAGGAAGTCTGACTGTAGACCCTAAGGCTCCCTG
CAACTTGCAAACAATAAAAAACTTGAGCTTGTATGTTGATCCATTGAG
GTTAGTGCCAATAAAACTTAGTTAAAAGTAGGACATGGATTAAAATATT
AGATGACAAAAGTGGTATAAGTGTAAAGAGCAAGAGAAGGGTTAACAT
TTTAACAGGGAAAGGAATAGGCAC TGAAAATTGCAAAATACAGATGGT
AGCAGCAGAGGAATTGGTATAAGTGTAAAGAGCAAGAGAAGGGTTAACAT
TTGACAATGATGGATACTGGTAGCATGGAACCCAAAGTATGACACGCGC
ACACTTTGGACAACACCAGACACATCTCCTAATTGCAGGATTGATAAGGA
GAAGGATTCAAAACTCACTTGGTACTTACAAAGTGTGGAAGTCAAATAT
TAGCTAATGTGTCTTGATTGTGGTGTCAAGGAAAATATCAATACATAGACC
ACGCTACAAATCCAAC TCTTAAATCATTTAAAATAAAACCTCTTTGATA
ATAAAGGTGTACTTCTCCAAGTTCAAAACCTGATTCCACATATTGGAACCT
TTAGAAGTGACAATTAACTGTATCTGAGGCATATAAAATGCAGTTGAA
TTTATGCCTAATTGGTAGCCTACCCAAAACCTACCACTGGCTCTAAAAAA
TATGCAAGGGATATAGTCTATGGAACATATATCTGGAGGTTGGCATA
TCAGCCAGTTGTAATTAAAGGTACTTTAATGAAGAAGCAGATAGTGTCA
CTCTATAACATTGAATTGTATGGAATAAAGAATATGCCAGGGTTGAA
TTTGAAACCACTTCCCTTACCTTCTCCTATATTGCCCAACAATAA

SEQ ID NO:2

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Penton17.Seq Length: 1554

1 ATGAGGCCTG CGGTGGTGT C TTCCCTCTCCT CCTCCCTCGT ACGAGAGCGT
 51 GATGGCGCAG GCGACCCCTGG AGGTTCCGTT TGTGCCTCCG CGGTATATGG
 101 CTCCTACGGA GGGCAGAAC AGCATTGTT ACTCGGAGCT GGCTCCGTTG
 151 TAGGACACCA CTCGCGTGT A CTTGGTGGAC AACAAAGTCGG CGGACATCGC
 201 TTCCCTGAAC TATCAAAACG ACCACAGCAA CTTCCGTGACC ACAGGTGGTGC
 251 AGAACACGA TTTCACCCCCC GCCGAGGCTA GCACCGAGAC GATAAATT
 301 GACGAGCGT CGCGGTGGGG CGGTGATCTG AAGACCATTC TGCACACCAA
 351 CATGCCAAT GTGAACGAGT ACATGTTCAC CAGCAAGTTT AAGGCGCGGG
 401 TGATGGTGGC TAGAAAACAC CCACAGGGGG TAGAAGCAAC AGATTTAAC
 451 AAGGATATCT TAGAGTATGA GTGTTTGAG TTTACCCCTGC CCGAGGGCAA
 501 CTTTCCGAG ACCATGACCA TAGACCTGAT GAACAAACGCC ATCTTGGAAA
 551 ACTACTTGCA AGTGGGGCGG CAAAATGGCG TGCTGGAGAG CGATATTGGA
 601 GTCAAGTTG ACAGCAGAAA TTTCAAGCTG GGCTGGGACC CTGTGACCAA
 651 GCTGGTGATG CCAGGGGTCT ACACCTACGA GGCTTTCAC CCGGACGTGG
 701 TGCTGCTGCC GGGCTGCCGG GTGGACTTCA CAGAGAGCCG CCTGAGCAAC
 751 CTCCTGGGCA TTCGCAAGAA GCAACCTTC CAAGAGGGCT TCAGAATCAT
 801 GTATGAGGAT CTAGAAGGGG GCAACATCCC CCCCTGCTG GATGTGCCA
 851 AGTACTTGGG AAGCAAGAAC AAGTTAGAGG AGGCATTGGA GAATGCTGCT
 901 AAAGCTAATG GTCTGCAAG AGGAGACAGT AGCGTCTCAA GAGAGGTTGA
 951 AAAGGCAGCT GAAAAAGAAC TTGTTATTGA GCCCATCAAG CAAGATGATA
 1001 CCAAGAGAAC TTACAACCTC ATCGAGGGAA CCATGGACAC GCTGTACCGC
 1051 AGCTGGTACC TGTCTATAC CTACCGGGAC CCTGAGAACG GGGTGCAGTC
 1101 GTGGACGCTG CTCACCACCC CGGACGTAC CTGCGGCCGG GAGCAAGTCT
 1151 ACTGGTCCT GCGGACCTC ATGCAAGAAC CCGTCACCTT CCGTTCTACC
 1201 CAGCAAGTC GCAACTACCC CGTGGTCGGC GCCGAGCTCA TGCCCTCCG
 1251 CGCCAAGAGC TTTTACAACG ACCTCGCCGT CTACTCCCAG CTCATCCGCA
 1301 GCTACACCTC CCTCACCCAC GTCTCAACC GCTTCCCCGA CAACCAGATC

SEQ ID NO: 3

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1351 CTCTGCCGTC CGCCCGCGCC CACCATCACC ACCGTCAGTG AAAACGTGCC
1401 TGCTCTCAC A GATCACGGGA CGCTACCGCT GCGCAGCAGT ATCCGCGGAG
1451 TCCAGCGAGT GACCGTCACT GACGCCCGTC GCCGCACCTG TCCCTACGTC
1501 TACAAGGCC C TGGGCATA GT CGCGCCGCGT GTGCTTTCCA GTCGCACCTT
1551 CTAA

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Claims

1. A chimeric adenoviral vector comprising nucleotide sequence of a first adenovirus, wherein at least one gene of said first adenovirus encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by the corresponding gene from a second adenovirus belonging to subgroup D, said vector further comprising a transgene operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell.
2. A chimeric adenoviral vector according to Claim 1 wherein said second adenovirus is selected from the group consisting of Ad 9, Ad 15, Ad 17, Ad 19, Ad 20, Ad 22, Ad 26, Ad 27, Ad 28, Ad 30, and Ad 39.
3. A chimeric adenoviral vector according to Claim 1 wherein said first adenovirus is selected from the group consisting of Ad 2, Ad 5, and Ad 12.
4. A chimeric adenoviral vector according to Claim 1 wherein said replaced gene encodes Ad fiber.
5. A chimeric adenoviral vector according to Claim 1 wherein said replaced gene encodes Ad penton base.
6. A chimeric adenoviral vector according to Claim 1 wherein a first replaced gene encodes Ad fiber, and a second replaced gene encodes Ad penton base.
7. A chimeric adenoviral vector comprising nucleotide sequence of a first adenovirus, wherein a portion of a gene thereof encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization

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thereof within said cell, is replaced by a portion of the corresponding gene from a second adenovirus belonging to subgroup D, said vector further comprising a transgene operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell.

5

8. A chimeric adenoviral vector according to Claim 7 wherein the encoding sequence that is replaced codes for a portion of Ad fiber.

9. A chimeric adenoviral vector according to Claim 7 wherein the encoding sequence that is replaced codes for a portion of Ad penton base.

10. A chimeric adenoviral vector according to Claim 9 wherein the encoding sequence that is replaced codes for an amino acid sequence that includes RGD.

- 15 11. A method of providing a biologically active protein to the airway epithelial cells of a patient comprising administering to said cells an adenoviral vector selected from the group consisting of:
 - (a) a chimeric adenoviral vector comprising nucleotide sequence of a first adenovirus, wherein at least one gene of said first adenovirus encodes a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by the corresponding gene from a second adenovirus belonging to subgroup D, said vector further comprising a transgene encoding said protein that is operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell; and
 - (b) a chimeric adenoviral vector comprising nucleotide sequence of a first adenovirus, wherein a portion of a gene thereof encoding a protein that facilitates binding of said vector to a target mammalian cell, or internalization thereof within said cell, is replaced by a portion of the

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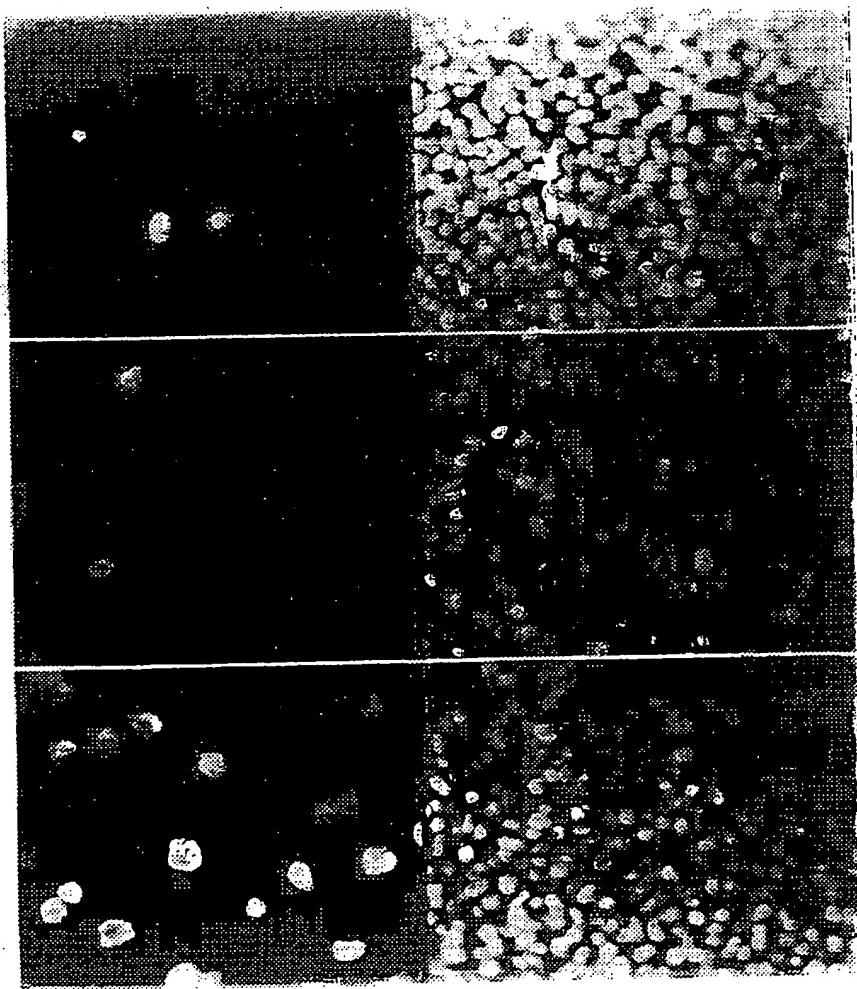
corresponding gene from a second adenovirus belonging to subgroup D, said vector further comprising a transgene encoding said protein that is operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell;

5 under conditions whereby the transgene encoding said protein is expressed, and phenotypic benefit is produced in said airway epithelial cells.

12. A method according to Claim 11 wherein said second adenovirus is Ad 17 and the nucleotide sequence thereof used in replacement of nucleotide sequence of said first adenovirus encodes a polypeptide selected from the group consisting of Ad 17 fiber, a fragment of Ad 17 fiber, Ad 17 hexon, a fragment of Ad 17 hexon, Ad penton base, and a fragment of Ad 17 penton base.
13. A method of providing a biologically active protein to the airway epithelial cells of a patient that comprises administering to said cells an adenoviral vector comprising elements of an Ad 17 genome, and a transgene encoding said protein that is operably linked to a eucaryotic promoter to allow for expression therefrom in a mammalian cell, under conditions whereby the transgene encoding said protein is expressed, and phenotypic benefit is produced in said airway epithelial cells.

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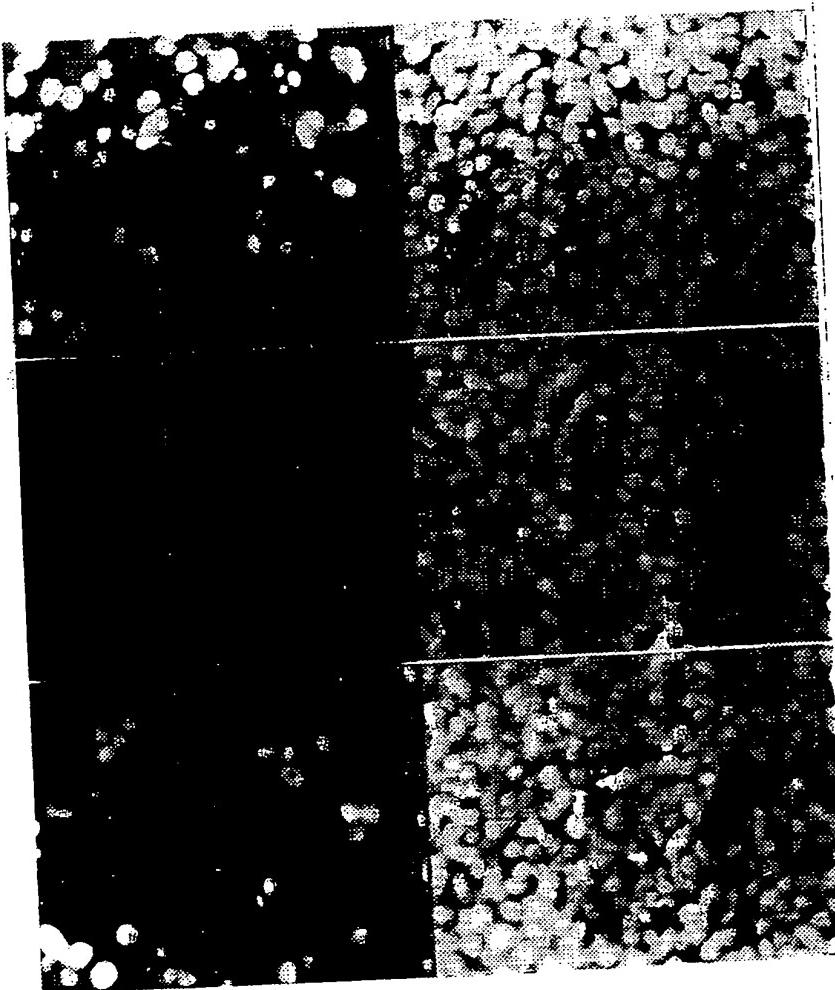
FIG. 1



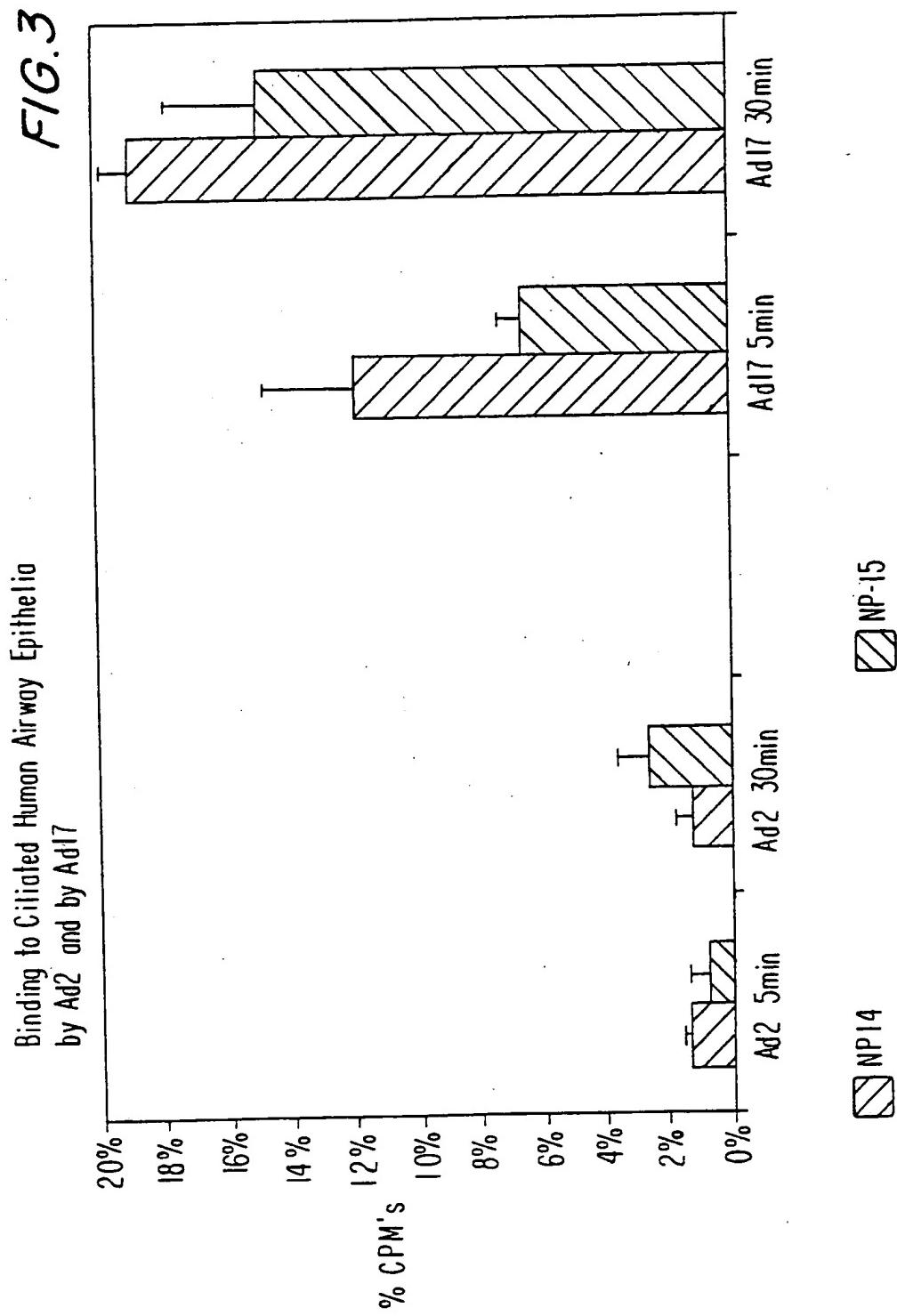
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FIG. 2



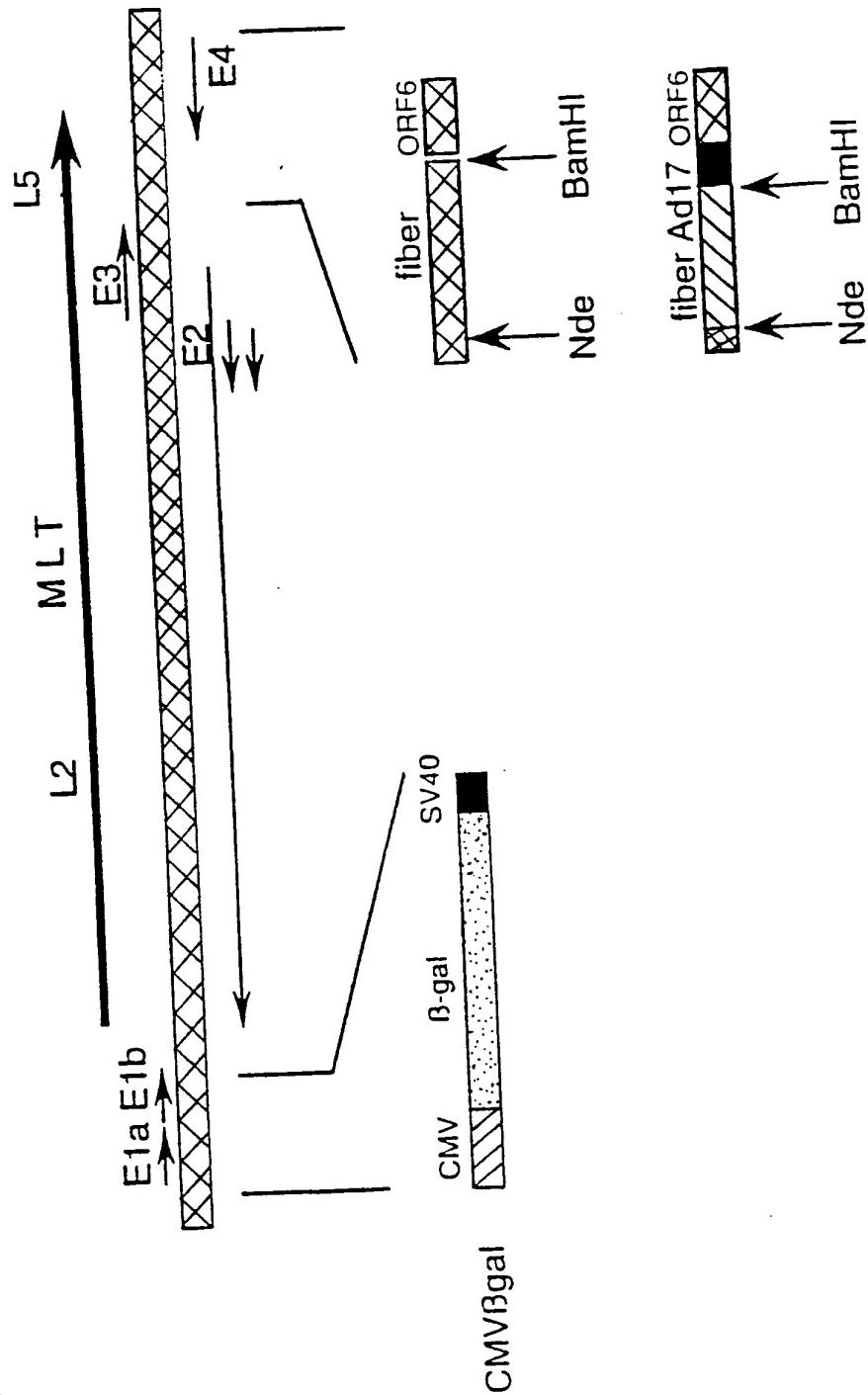
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Chimeric Ad2/βgal-2/ Ad17 vectors

FIG. 4



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FIG. 5A-1

1 M RRAVVSSSSPPPSYESVMA QATLEVPFVPPRYMAPTEGR 39 SEQ ID NO:4
 | | : | | | | | : | | : | | | | | : | | : | | | | | : | |
 1 M0 RAAMYEEGPPPSYESVVAAPVAAALGSPFDAPLDPPFVPPRYLRTGGR 52 SEQ ID NO:5

 40 NSIRYSELAPLYDTTRVYLVDNKSA DIASLNYQNDHSMNFLTTVVONINDFT 89
 | | | | | | | : | | | | | | | | | | | | | | | | | | | | | | : | |
 53 NSIRYSELAPLFDTTRVYLVDNKSTDVASLNYQNDHSMNFLTTVIQNNDYS 102

 90 PAEASTQTINFDERSRWGGDLKTILHTNMPNVNEYMFITSKFKARVMVARK 139
 | | | | | | | : | | | | | | | | | | | | | | | | | | | | | | | : | |
 103 PGEASTQTINLDDRSHWGGDLKTILHTNMPNVNEFMFTNKFKARVMVSRS 152

 140 HPQGVVEATDL SKDILEYEWFEFTLPEGNFSETMTIDLMNNAILENYLQVG 189
 | | | | | | | : | | | | | | | | | | | | | | | | | | | | | | | : | | |
 153 LTKDKQVE LKYEWFEFTLPEGNYSETMTIDLMNNAIIVEHYLKVG 196

 190 RQNGVILESDIGVKFD SRNF KLGWD DPVTKL VMPGVYTYEA FHPDVVLLPGC 239
 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | : | | |
 197 RQNGVILESDIGVKFD TRNF RLGFDPVTGL VMPGVYTN EA FHPDILLPGC 246

FIG. 5A-2

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FIG. 5B

393	DPVTFRSTQQVSNYPVVGAEIIMPFRAKSFYNDLAVYSQLIRSYTSLTHVF	442
447	DPVTFRSTSQISNFPVVGAEIILPVHKSFYNDQAVYSQLIRQFTSLTHVF	496
443	NRFPDNQILCRPPAPTTVSENVPALTDHGTLPLRSSSIRGVQRVTITDA	492
497	NRFPENQILARPPAPTTVSENVPALTDHGTLPLRNSIGGVQRVTITDA	546
493	RRRTCPYYKALGIVAPRVLSSRTF	517
547	RRRTCPYYKALGIVSPRVLSSRTF	571

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FIG. 6A-1

1	Penton5 Penton2 Penton3 Penton12 Penton40 Penton17 Pentonf10	... MERAAM. MQRAAM. MRRRAVLG GAV. VYPEGP ... MRRRAVEL QTV. APPETP ... MRRAVGV PPVMAAYAEGP ... MRRRAVV. MWGLQPPTSI	YEEGP PPSYESVUSA YEEGP PPSYESVUSA PPSYESVM PPSYESVM PPSYETVM PPSYETVM PPSYESVM PPSYESVM PPSYESVM PSSSP PPPPPTELT	... APVAAALG SPFDAPLDPP-SEQ ID NO:6 ... APVAAALG SPFDAPLDPP-SEQ ID NO:5 ... AMIQOPPLEAP-SEQ ID NO:7 ... AAAPP-SEQ ID NO:8 ... ADLPATLQAL-SEQ ID NO:9 ... QATLEVVP-SEQ ID NO:4 ... A... YPPPAASAQS CSSSGGQSEL-SEQ ID NO:10	50
51	Penton5 Penton2 Penton3 Penton12 Penton40 Penton17 Pentonf10	FVP. PRYLRP TGGRNSIRYS FVP. PRYLRP TGGRNSIRYS FVP. PRYLAP TEGRNSIRYS YVP. PRYLGP TEGRNSIRYS HVP. PRYLGP TEGRNSIRYS FVP. PRYMAP TEGRNSIRYS YMLQRVMAP	ELAPLFDTTR VYLVDNKSTD ELAPLFDTTR VYLVDNKSTD DVSPLYDTTK LYLVVDNKSAD ELSPLYDTTR VYLVDNKSSD ELAPFLDTTR VYLVDNKSAD VYLVDNKSAD DYTPCRNTIK	VASLNYQNDH VASLNYQNDH IASLNYQNDH IASLNYQNDH IASLNYQNDH IASLNYQNDH IASLNYQNDH	100

FIG. 6A-2

101
 Penton5 SNFLTTVQN NDYSPGEAST QTINLDDRSH WGGDLKTILH TNMPNVNEFM
 Penton2 SNFLTTVQN NDYSPGEAST QTINLDDRSH WGGDLKTILH TNMPNVNEFM
 Penton3 SNFLTTVQN NDFTPTTEAST QTINFDERSR WGGQLKTIMH TNMPNVNEYM
 Penton12 SNFLTTVQN NDYSPIEAGT QTINFDERSR WGGDLKTILH TNMPNVNDFM
 Penton40 SNFQTTVQN NDFTPTTEAGT QTINFDDRSR WGGDLKTILR TNMPNINEFM
 Penton17 SNFLTTVQN NDFTPAAEAST QTINFDERSR WGGDLKTILH TNMPNVNEYM
 Pentonf10 SNFRRTVQH QDLDADTAAT ESIQLDNRSC WGGDLKTAVR TNCPNVSSFF

150
 Penton5 FTNKFKARVM VSRL. PTKD. . N QVELKYEWVE FTLPEGNYSE
 Penton2 FTNKFKARVM VSRS. LTKD. . K QVELKYEWVE FTLPEGNYSE
 Penton3 FSNKFKARVM VSRKAPEGVT VNDDTYDH. . K EDILKYEWFE FILPEGNFSA
 Penton12 FTTKFKARVM VARK. TNNE. . G QTILEYEWAE FVLPEGNYSE
 Penton40 STNKFRARVM VEK. VNR. . K TNAPRYEWFE FTLPEGNYSE
 Penton17 FTSKFKARVM VARKIIPQGV. . EATDL. . S KDILEYEWFE FTLPEGNFSE
 Pentonf10 QNSVRRMM WKRDPPPTSTA PPSAVGSGYS VPGAQYKWD LTVPEGNYAL

151
 Penton5 FTNKFKARVM VSRL. PTKD. . N QVELKYEWVE FTLPEGNYSE
 Penton2 FTNKFKARVM VSRS. LTKD. . K QVELKYEWVE FTLPEGNYSE
 Penton3 FSNKFKARVM VSRKAPEGVT VNDDTYDH. . K EDILKYEWFE FILPEGNFSA
 Penton12 FTTKFKARVM VARK. TNNE. . G QTILEYEWAE FVLPEGNYSE
 Penton40 STNKFRARVM VEK. VNR. . K TNAPRYEWFE FTLPEGNYSE
 Penton17 FTSKFKARVM VARKIIPQGV. . EATDL. . S KDILEYEWFE FTLPEGNFSE
 Pentonf10 QNSVRRMM WKRDPPPTSTA PPSAVGSGYS VPGAQYKWD LTVPEGNYAL

200 ^{9/28}
 Penton5 TMTIDLMNA IVEHYLKVG GR QNGVLES DIG VKFDTRNFR L GFDPVTGLVM

250

201

Penton5

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FIG. 6B-1

Penton2	TMTIDLMNNA	IYEHYLKVGR	QNGVLESDIG	VKFDTRNFRL	GFDPTVTGLVM
Penton3	TMTIDLMNNA	IIDNYLEIGR	QNGVLESDIG	VKFDTRNFRL	GWDPETKLIM
Penton12	TMTIDLMNNA	IIEHYLRVGR	QHGVLESDIG	VKFDTRNFRL	GWDPETQLVT
Penton40	TMTIDLMNNA	IVDNYLAUGR	QNGVLESDIG	VKFDTRNFRL	GWDPTVKLVM
Penton17	TMTIDLMNNA	ILENYLQVGR	QNGVLESDIG	VKFDTSRNFKL	GWDPTVKLVM
Pentonf10	CELDLLNEG	IVQYLSEGR	QNNVQKSDIG	VKFDTRNFGF	LRDPVTGLVT
				300	
Penton5	PGVYTNEAFH	PDIILLPGCG	VDFTHSRLSN	LLGIRKRQPF	QEGFRITYDD
Penton2	PGVYTNEAFH	PDIILLPGCG	VDFTHSRLSN	LLGIRKRQPF	QEGFRITYDD
Penton3	PGVYTNEAFH	PDIVLLPGCG	VDFTESRLSN	LLGIRKRHPF	QEGFKIMYED
Penton12	PGVYTNEAFH	PDIVLLPGCG	VDFTESRLSN	ILGIRKRQPF	QEGFVIMYEH
Penton40	PGVYTNEAFH	PDIVLLPGCG	VDFTESRLLN	LLGIRKRMPF	QKGFQIMYED
Penton17	PGVYTNEAFH	PDVVLLPGCG	VDFTESRLLN	LLGIRRKQPF	QEGFRIMYED
Pentonf10	PGTYVYKGYH	PDIVLLPGCA	IDFTYSRLSL	LLGIGKREPY	SKGFVITYED

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F/G. 6B-2

301

Penton5 LEGGNIPALL DV DAYQASLK DD TEQGGGA GGSN SSGSA EENS NAAAAA
 Penton2 LEGGNIPALL DV DAYQASLK DD TEQGGDGA GGGNNSSGA EENS NAAAAA
 Penton3 LEGGNIPALL DVTAYEESKK DTTTETTTLA VAEETSE
 Penton12 LEGGNIPALL DVKKYENSL Q
 Penton40 LEGGNIPALL DV EKYEASIK
 Penton17 LEGGNIPALL DV PKYLESKK KLE E ALENAAK
 Pentonf10 LQGDDIPALL DLDSVDVND A DGEVIELDNA A

351

Penton5 MQPVEDMNDH AIRGDTFATR AEEKRAEEA AEEAAAPAAQ PEVEKPQKKP
 Penton2 MQPVEDMNDH AIRGDTFATR AEEKRAEEA AEEAAAPAAQ PEVEKPQKKP
 Penton3 DDD ITRGDTYITE KQKREAAAE V KKEL
 Penton12 DQN TVRGDNFIA L NKAA
 Penton40 EAQ EIRGADEFKPN PQ DL
 Penton17 ANG PARGDSSVSR EVEKAA EKEL
 Pentonf10 .

400

Penton5 MQPVEDMNDH AIRGDTFATR AEEKRAEEA AEEAAAPAAQ PEVEKPQKKP
 Penton2 MQPVEDMNDH AIRGDTFATR AEEKRAEEA AEEAAAPAAQ PEVEKPQKKP
 Penton3 DDD ITRGDTYITE KQKREAAAE V KKEL
 Penton12 DQN TVRGDNFIA L NKAA
 Penton40 EAQ EIRGADEFKPN PQ DL
 Penton17 ANG PARGDSSVSR EVEKAA EKEL
 Pentonf10 .

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FIG. 6B-3

450

401 VIKPLTEDSK KRSYNLI... SNDSTFTQYR SWYLAYNYGD PQTGIRSWTL
 Penton5 VIKPLTEDSK KRSYNLI... SNDSTFTQYR SWYLAYNYGD PQTGIRSWTL
 Penton2 VIKPLTEDSK KRSYNLI... E.DKINTAYR SWYLSYNYGN PEKGIRSWTL
 Penton3 KIOPPLEKDSK SRSYNVL... P.DKKNTKYR SWYLAYNYGD PEKGVRSWTL
 Penton12 RIEPVETDPK GRSYNLL... EGDKNNNTAYR SWFLAYNYGD AEKGVKSWTL
 Penton40 EIVPVEKDSK ERSYNLL... E.GTMDTLYR SWYLSYTYYRD PENGVQSWTL
 Penton17 VIEPIKQDDT KRSYNLI... E.GTGKPVTAZR SWMLAYNVPN SQANQT.. TL
 Pentonf10 ... PLLHDSA GVSYNVIYDQ VTGKPVTAZR SWMLAYNVPN SQANQT.. TL

500

451 LCTPDVTCGS EQVYWSLPPDM MQDPVTFRST RQISNFPVVG AELLPVHSKS
 Penton5 LCTPDVTCGS EQVYWSLPPDM MQDPVTFRST SQISNFPVVG AELLPVHSKS
 Penton2 LCTSDVTCGA EQVYWSLPPDM MQDPVTFRST RQVNYYPVVG AELMPVF SKS
 Penton3 LTTPDVTCGS EQVYWSLPPDM MQDPVTFRSS RQVSNNYPVVA AELLPVHAKS
 Penton12 LTTPDVTCGS EQVYWSLPPDM MQDPVTFRPS TQVSNYPVVG VELLPPVHAKS
 Penton40 LTTPDVTCGS QQVYWSLPPDM MQDPVTFRST QQVSNNYPVVG AELMPFRAKS
 Penton17 LTTPDVTCGA EQVYWSLPPDL MQDPVTFRST FIAPTGFKE D MNLFPTYNKI
 Pentonf10 LTVPDMAAGGI GAMYTSLPPDT FIAPTGFKE D NTTNLCPVVG

500

501 FYNDQAVYYSQ LIRQFT.SLT HVFNRFPENQ ILARPAPTI TTVSENVPAL
 Penton5 FYNDQAVYYSQ LIRQFT.SLT HVFNRFPENQ ILARPAPTI TTVSENVPAL
 Penton2 FYNDQAVYYSQ LIRQFT.SLT HVFNRFPENQ ILIRPPAPTI TTVSENVPAL
 Penton3 FYNEQAVYYSQ QLRQAT.ALT RVFNRFPENQ ILVRPPAATI TTVSENVPAL
 Penton12 FYNEQAVYYSQ LIRQST.ALT

550

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FIG. 6C

Penton40	FYNEQAVYSQ	LIRQST. ALT	HIFNRFPENQ	ILVRPPAPTI	TTVSENVPAL	
Penton17	FYNDLAVYSQ	LIRSYT. SLT	HVFNRFPDNQ	ILCRPPAPTI	TTVSENVPAL	
Pentonf10	YYQAASYTVQ	RLENSCQSAT	AAFNRFPENE	ILKQAPPMMNV	SSVCDNQPAV	
						600
Penton5	TDHGTLPLRN	SIGGVQRVTI	TDARRRTCPY	VYKALGIVSP	RVLSRSRTF*	
Penton2	TDHGTLPLRN	SIGGVQRVTI	TDARRRTCPY	VYKALGIVSP	RVLSRSRTF*	
Penton3	TDHGTLPLRS	SIRGVQRVTV	TDARRRTCPY	VYKALGIVAP	RVLSRSRTF*	
Penton12	TDHGTLPLRS	SISGVQRVTI	TDARRRTCPY	VYKALGIVSP	RVLSRSRTF*	
Penton40	TDHGTLPLRS	SISGVQRVTI	TDARRRTCPY	VHKALGIVAP	KVLSRSRTF*	
Penton17	TDHGTLPLRS	SIRGVQRVTV	TDARRRTCPY	VYKALGIVAP	RVLSRSRTF*	
Pentonf10	VQQGVLPVKS	SLPGLQRVLI	TDDQRRIPY	VYKSIATVQP	TVLSSATLQ*	
						551

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FIG. 7A-1

Fiber17.Pep x Fiber2.Pep

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FIG. 7A-2

145 NLQNTD . . . GSSRGIGISVRARE 164
| : | | : | : | : | : | : |
301 YNRGLYLFNASNNTKKLEVSIIKKSSGLNFDNTAIAINAGKGLEFDTNTSE 350
| : | | : | : | : | : |
165 GLTFDNDGYLVAWNPKYDTRT 185
| : | | : | : | : | : |
351 SPDINPIKTKIGSGIDYNENGAMITKLGAGLSFDNSGAITIGNKNDDKLT 400
| : | | : | : | : | : |
186 LWTTTPDTSPNCRIDKEKDSSLTLVLTCKGSQILANVSLIVVSGKXYQYIDH 235
| : | | : | : | : | : | : | : | : | : | : |
401 LWTTTPDPSPNCRIHSNDCKFTLVLTKGSQVLATVAALAVSGDLS . . . 446

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FIG. 7B

				ATNPTLKSFKIKLLFDNKGVLLPS SNLDSTYWNFRSDNLTVSEAYKNAVE	285
236	ATNPTLKSFKIKLLFDNKGVLLPS SNLDSTYWNFRSDNLTVSEAYKNAVE				
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247	SMTGTVASVSIFLRFQDNGVLMENSSLKKHYWNFRNGNSTNANPYTNAVGC	496			
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286	FMPNLVAYPKPTTGSKKYARDIVYGNIIYLGGLAYQPVVVIKVTFNEEAD.	543			
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334	SAYSITFEFVWNKE.YARVEFETTSFTFSYIAQQ	366			
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354	ETSEVSTYSMSFTWSWESGKYTTETEATNSYTFSYIAQE	582			
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FIG. 8A-1

	1	50
8 fiber	MTKRLRA.	EDDEN PVIPIGYARN Q. NIPFLTPP FVSSNGFQNF
9 fiber	MSKRLRV.	EDDEN PVVPGYARN Q. NIPFLTPP FVSSDGFQNF
15 fiber	MSKRLRV.	EDDFN PVVPGYARN Q. NIPFLTPP FVSSDGFQNF
17 fiber	MSKRLRV.	EDDFN PVVPGYARN Q. NIPFLTPP FVSSDGFKNF
2 fiber	MKRARP.	SEDTEN PVVPGYDTETG PPTVFLTPP FVSPNGFOES
5 fiber	MKRARP.	SEDTEN PVVPGYDTETG PPTVFLTPP FVSPNGFOES
4 fiber	MSKSARG.	WSDGFD PVVPYDADND RP. CPSSTLP SFSSDGFOEK
40-1 fiber	MKRTTRIE.	DDEN PVVPYD. TSS TPSIPIVAPP FVSSDGLOQEN
41 fiber	MKRTTRIE.	DDEN PVVPYD. TFS TPSIPIVAPP FVSSDGLOQEK
40-2 fiber	MKRARFE.	DDFN PVVPYE. HYN PLDIPIFITPP FASSNGLQEK
12 fiber	.MKRSRTQYA	EETEEENDDFN PVYPFD. PFD TSDVPFVTTP FTSSNGLQEK
3 fiber	MAKRARL.	STSFn PVVPYEDESS SQH. PFINPG FISPDGFTQS

FIG. 8A-2

51 8 fiber 9 fiber 15 fiber 17 fiber 2 fiber 5 fiber 4 fiber 40-1 fiber 41 fiber 40-2 fiber 12 fiber 3 fiber	<p>100 SEQ ID NO:13</p> <p>PPGVLSLKLA DPITIN . NQN VSLKVGGGLT LQEET PPGVLSLKLA DPIAV . NGN VSLKVGGGLT LQDGT PPGVLSLKLA DPIAIA . NGN VSLKMGGGLT LQEQT PPGVLSLKLA DPITIA . NGD VSLKVGGGLT LQE PPGVLSLRVS EPLDTS . HGM LAKMGSGLT LDKGAGNLTSQ NVTTVTQPLK SEQ ID NO:12 PPGVLSRLS EPLVTS . NGM LALKMGNGLS LDEAGNLTSQ NVTTVSPPLK SEQ ID NO:16 PPGVLSRLS EPLVTS . NGM LALKMGNGLS LDEAGNLTSQ NVTKAIAPL SEQ ID NO:17 PLGVLSLGPV RPCHTK . NGE ITLKLGEGVD LDDSGKLIAN TVNKAIAPL PLGVLSLGPV RPCHTK . NGE ITLKLGSNIT LQ . NGLLSA PPGVLAALKYT DPITTNAKHE LTLKLGSNIT LQ . NGLLSA PPGVLAALKYT DPITTNAKHE LTLKLGSNIT LE . NGLLSA PPGVLSLKYT DPLTTK . NGA LTLKLGTGLN IDKNGDLSSD ASVEVVSAPIT SEQ ID NO:20 PPGVLSLKYT DPLTTK . NGA LTLKLGTGLN IDKNGDLSSD ASVEVVSAPIT SEQ ID NO:21 PPGVLAALNYK DPIVTE . NGT LTLKLGDGIK LNAQGQLTAS NNINVLEPLT SEQ ID NO:22 PPGVLAALNYK DPIVTE . NGT LTLKLGDGIK LNAQGQLTAS NNINVLEPLT SEQ ID NO:22 PNGVLSLKCVR NPLTTA . SGS LQLKVGSGLT VD</p> <p>150</p>
	<p>101 8 fiber 9 fiber 15 fiber 17 fiber</p>

FIG. 8B-1

2fiber	KTKSNISLDT	FAPLTITSGA	LTVATTAPLI	VTSGALSQS	QAPLTVQDSK
5fiber	KTKSNINLEI	SAPLTVTSEA	LTVAAAAPLM	VAGNTLTMQS	QAPLTVHDSK
4fiber	.	.	.	SFFQQH	HFPL...
40-1fiber
41fiber
40-2fiber	KTNKIVGLNY	TKPLALQNNIA	LTLSYNAPFN	VVNINNLAINM	SQPVTII
12fiber	NtSQGILKLSW	SAPLAVKASA	LTLNTRAPLT	TTDESLALIT	APPITVESSR
3fiber
151					
8fiber
9fiber
15fiber
17fiber
2fiber
5fiber
4fiber
40-1fiber
41fiber
40-2fiber	NANNELSLL	IDAPLNAADTG	TLRLRSDAPL	GLVVDK.TLKV	
12fiber	LGLATIAPLS	LDGGGNLGLN	LSAPLDVSNN	NLHLTTETPL	VVNSSGALSV
3fiber

FIG. 8B-2

201	250	20/28
8fiber	GKLTVNTEPPLH	
9fiber	GNLTVNADPPLQ	
15fiber	GSLTVDPKAPLQ	
17fiber	GSLLT	TGSLGINMED
2fiber	LSGSDSDTLT	TGSLGIDLKE
ATKGPITVSD	ITASPPPLTTA	
ATQGPLTVSE	ITASPPPLTTA	
5fiber	LYTPKMEMYP	KSTI
4fiber	YKFLLPPLSIL	
	TWIP	NNSLGLATSA
	VSPPLTNS	
	TVPT	VSPPLTNS
40-1fiber	TVPT	NNSLGLATSA
41fiber	NFLTLAIERP	LKYSPPLKIE
40-2fiber	LFSSPLYLDN	NENLTLSSTGG
12fiber	NALTLPADP	LALSSNRAVA
3fiber	ATADPISVRN	LMVSSD.GLG

FIG. 8B-3

FIG. 8C-1

FIG. 8C-2

401	GTDLSNNGG.	NICVRVG	E.....	GGGLS	FNDNGDLVAF
8 fiber	GTESTDNGG.	TVCVRVG	E.....	GGGLS	FNNDGDLVAF
9 fiber	GTDITDNGG.	SIRVRVG	E.....	GGGLS	FNEAGDLVAF
15 fiber	GTNLQNTDG	SSRGIGISVR	A.....	REGLT	FDNDGYLVAW
17 fiber	EFDTNTSESP	DINPIKTKIG	SGIDYNNENGA	MITKLGAGLS	FDNSGAITIG
2 fiber	EFG..SPNAP	NTNPLKTKIG	HGLEFDSNKA	MVPKLGTGLS	FDSTGAITVG
5 fiber	RFGTSSSTEG	VNNAYPIOV.	KLGSGLS	FDSTGAIMAG
4 fiber
40-1 fiber	LE	LNVKLGSCQLQ	FDNNNGRITIS
41 fiber	LE	LNVKLGSCQLQ	FDSNGRIAIS
40-2 fiber	ASALIMMSGVT	QTLNVNANTS	KGLAIENNNS.	LUVKLGNGLR	FDSWGSIAVS
12 fiber	EKGLMFSGN	QIALNAG	QGLTFNNQ.	LRVKLGAGLI	FDSSNNIALG
3 fiber	KLGNGLT	FDSSNSIAALK

FIG. 8C-3

500

451	NKKEDK.. . .	RTLWTTTPDT	SPNCRID.. . .	QDKDSKLSSLV	LTKCGSQILA
8 fiber	NKKEDK.. . .	RTLWTTTPDT	SPNCKID.. . .	QDKDSKLTLV	LTKCGSQILA
9 fiber	NKKEDM.. . .	RTLWTTTPDP	SPNCKII.. . .	EDKDSKLTLI	LTKCGSQILA
15 fiber	NPKYDT.. . .	RTLWTTTPDT	SPNCRID.. . .	KEKDSKLTLV	LTKCGSQILA
17 fiber	NKNDDK.. . .	LTLWTTTPDP	SPNCRIH.. . .	SDNDCKFTLV	LTKCGSQILA
2 fiber	NKNNDK.. . .	LTLWTTTPAP	SPNCRLN.. . .	AEKDAKLTLV	LTKCGSQILA
5 fiber	NKNNDK.. . .	LTLWTTTPDP	SPNCQIL.. . .	AENDAKLTLCL	LTMCDSQILA
4 fiber	NKDYDK.. . .	LTLWTTTPDP	TPNCSIY.. . .	ETQDANLFLC	LTKNGAHVLG ^{24/28}
40-1 fiber	NRIQTRSUTS	LTTIWSIS.. P	TPNCSIY.. . .	ETQDANLFLC	LTKNGAHVLG
41 fiber	NSNRTRSVPS	LTTIWSIS.. P	TPNCSIY.. . .	ESLDAKWLV	LVKCNGGIVNG
40-2 fiber	PTIT.. . P.	RTLWTTADP	SPNATFY.. . .	QELDAKLTLCL	LTKNGSIVNG
12 fiber	SSSNTPYDP..	LTLWTTPDPL	PPNCSLI.. . .	QNPDSKLTLI	LVKNGGIVNG
3 fiber	NN.. TLWTTGPKP	EANCIEYGR		

550

501	NVSLIVVAGR	YKIINNNNTNP	ALKGFTIK	LIFDKNGVLM	ESSN..
8 fiber	NVSLIVVDGK	YKIINNNNTQP	ALKGFTIK	LIFDENGVLM	ESSN..
9 fiber	SVSLLVVKGK	FSNINNTTNP	NEADKQITVK	LIFDANGVLK	QGST..
15 fiber	NVSLIVVSGK	YQYIDIATNP	TLKSFKIK	LIFDNKGVLL	PSSN..
17 fiber	TVAALAV.. S.	GDLSSM	TGTIVASVSIF	LRFDQNGVLM	ENSS..
2 fiber	TVSVLAV.. K.	GSLAPI	SCTVQSAHLI	IRFDENGVLL	NNSF..
5 fiber					

FIG. 8D-1

4 fiber	TVSVLVR.	GNLNPI	TGTVSSAQVF	LRFDANGVLL	TEHS.....	
40-1 fiber	TITIKGLKGA	LREMNDNA..	LSVK	LPFDNQGNLL	NCA.....	
41 fiber	TITIKGLKGA	LREMHDNA..	LSLK	LPFDNQGNLL	NCA.....	
40-2 fiber	TISIKAQKGT	LL..KPTASF	ISFV	MFYSDGWTWR	KNYPVFDNEG	
12 fiber	IVSLVGVKGN	LLNIQSTTT	VGVH	LVFDEQGRLLI	TSTP.....T	
3 fiber	YVTLMGASDY	VNTLFKNKVN	SINVE	LYFDATGHIL	PDSSSLKTDL	
							600
551	LGKSYWNF	RNQNSIMSTA	YEKAIGFMPN	LVAYPKPTTG	SKKY.....ARD		
8 fiber	LGKSYWNF	RNENSIMSTA	YEKAIGFMPN	LVAYPKPTAG	SKKY.....ARD		
9 fiber	MDSSYWNF	RSDNSNLSQP	YKKAVGFMPS	KTAYPKQTCKP	TNKIEISQAKN		
15 fiber	LDSTYWNF	RSDNLTVSEA	YKNAVEFMPN	LVAYPKPTTG	SKKY.....ARD		
17 fiber	LKKHYWNF	RNGNSTNANP	YTNAVGFMPS	LLAYPKTQSQ	T.....AKN		
2 fiber	LDPEYWNF	RNGDLTEGTA	YTNAVGFMPS	LSAYPKSHGK	T.....AKS		
5 fiber	TSKKYWG	KQGDSIDGTP	YTNAVGFMPS	STAYPKTQSS	T.....TKN		
4 fiber	LESSTWRY	QETNAVVA...	SNALTFMPN	STVYPRNKTA	D.....PGN		
40-1 fiber	LESSTWRY	QETNAVVA...	SNALTFMPN	STVYPRNKTA	H.....PGN		
41 fiber	ILANSATWGY	ROGOSANTN.	VSAVEFMPN	SKRYPNEKGS	E.....VQN		
40-2 fiber	ALVPQASWGY	RQQSVSTNT	VTNGLGFMPN	VSAYPRPNAS	E.....AKS		
12 fiber	ELKYKQTADFSARGFMPS	TTAYPFVLPN	AGTH...NEN		
3 fiber							

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650

601	IVYGNNTYLGG	KPHQ...	PVTI	KTTFNQETG.	CEYS	ITFDFSWAKT
8 fiber	IVYGNNTYLGG	KPDQ...	PVTI	KTTFNQETG.	CEYS	ITFDFSWAKT
9 fiber	KIVSNVYLGG	KIDQ...	PCVI	IIISFNEEAD.	SDYS	IVFYFKWYKT
15 fiber	IVYGNNTYLGG	LAYQ...	PVVI	KVTFNEEAD.	SAYS	ITFEFVNKE
17 fiber	NIVSQVYLNH	DKTK...	PMIL	TITLNGTSES	TETSEVSTYS	MSFTWSWESG	
2 fiber	NIVSQVYLNH	DKTK...	PVTL	TITLNGTQET	GDTT.	PSAYS	MSFSWIDWSGH
5 fiber	NIVSQVYLMG	DVSK...	PMLL	TITLNGTDDT	T.....	SAYS	MSFSYTWNTNG
4 fiber	NIVGQQVXMNG	QISP...	NITF	SVVYNEINS.	GYA	FTFKW.
40-1 fiber	MLI....	QISP...	NITF	SVVYNEINS.	GYA	FTFKW.
41 fiber	MLI....	QISP...	NITF	SVVYNEINS.	LEGYS	LKFTW.
40-2 fiber	MALTYTFLQG	DPM...	AISF	QSIYN..HA.	LNGYS	LTFMW.
12 fiber	QMVSLTYLQG	DTSK...	PITM	KVAFNGITS.	SGLS	
3 fiber	YIFGQCYYKA	SDGALFPLEV	TVMILNKRLPD	SRTSYVMTFL	WSLNAGLAPE		

FIG. 8D-2

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651	. YVNVEFETT	SFTFSYIAQE	*	.
	. YVNVEFETT	SFTFSYIAQE	*	.
8 fiber	. YVNVEFETT	SFTFSYIAQE	*	.
9 fiber	. YENVQFDSS	SFNFSYIAQQ	*	.
15 fiber	. YARVEFETT	SFTFSYIAQQ	*	.
17 fiber	. KYTTEFATN	SYTFSYIAQE	*	.
2 Fiber	NYINEIFATS	SYTFSYIAQE	*	.
5 fiber	SYIGATFGAN	SYTFSYIAQQ	*	.
4 fiber	GKPFHPP	TAVFCYITEQ	*	.
40-1 fiber	GKPFHPP	TAVFCYITEQ	*	.
41 fiber	: NERFDIP	CCSF SYVTEQ	*	.
40-2 fiber	NYINQPFSSTP	SCSF SYVTEQ	*	.
12 fiber	T.TQATLITS	PFTFSYIRED D*	*	.
3 fiber			*	.

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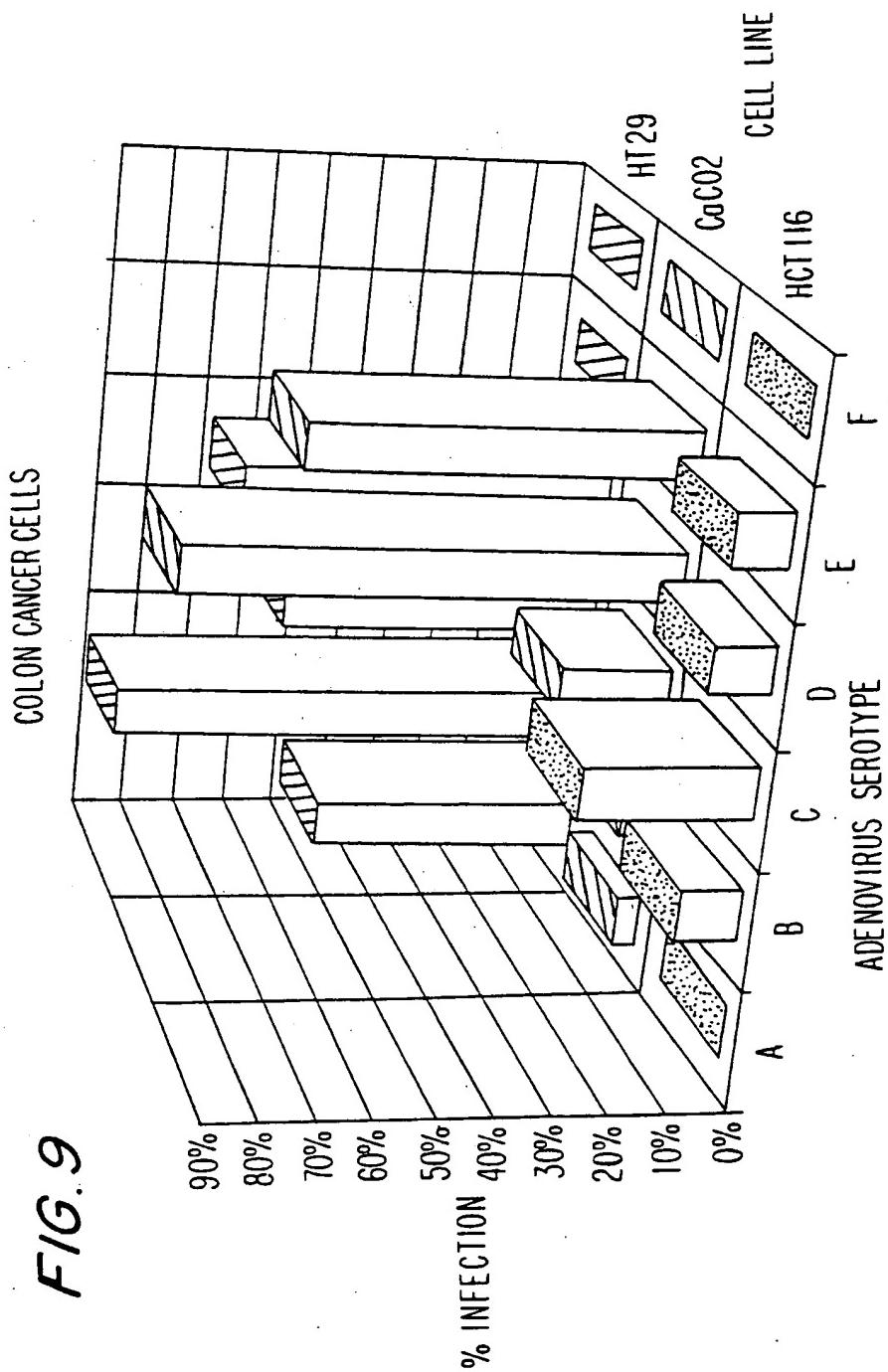
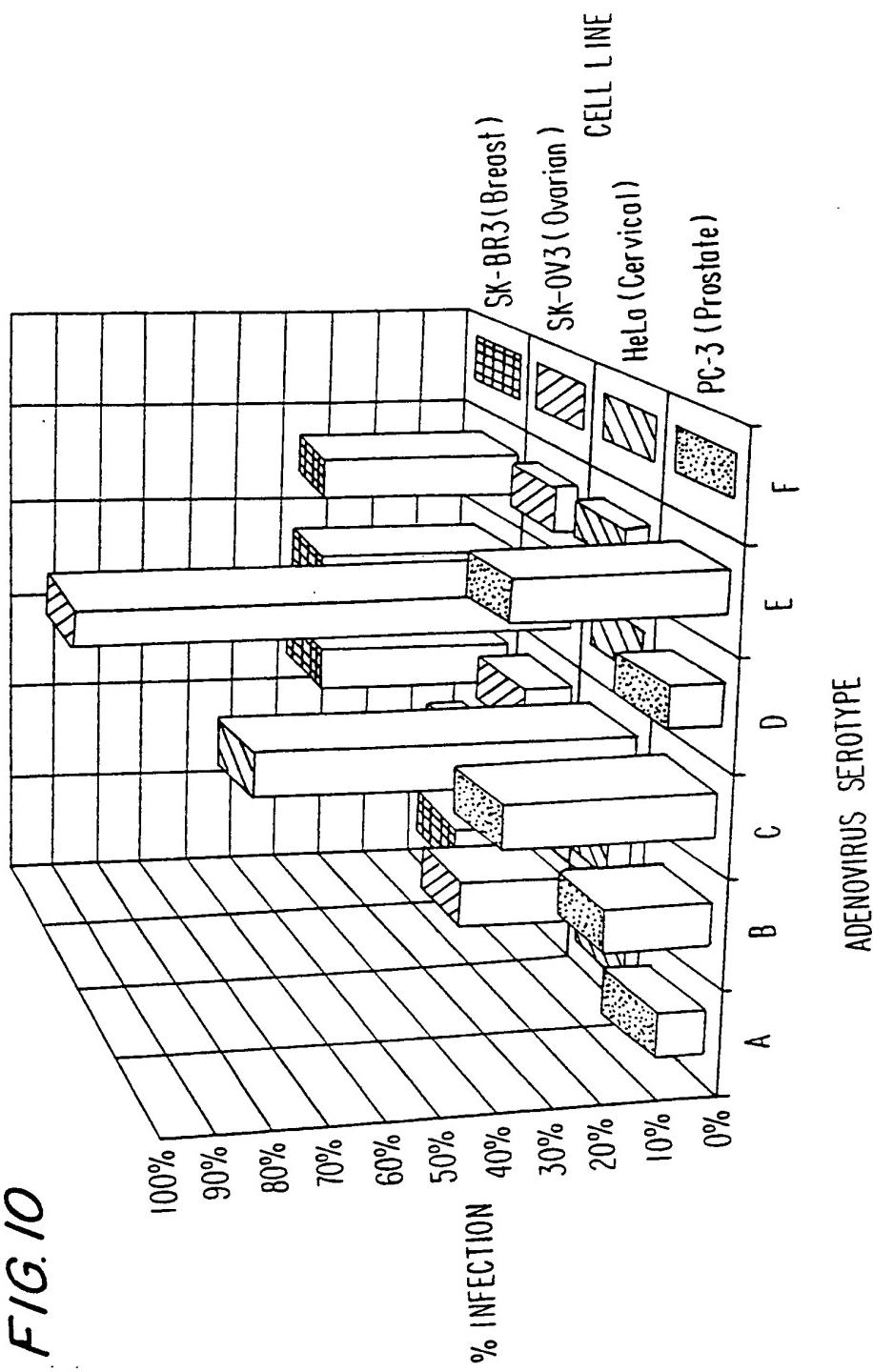


FIG. 9

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FIG. 10



INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/US 97/21494

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/86 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P.W. ROELVINK ET AL.: "Comparative analysis of adenovirus fiber-cell interaction: Ad2 and Ad9 utilize the same cellular fiber receptor but use different binding strategies for attachment" JOURNAL OF VIROLOGY, vol. 70, no. 11, November 1996, AMERICAN SOCIETY FOR MICROBIOLOGY US, pages 7614-7621, XP002062100 see page 7620, last paragraph ---	1-13
A	WO 96 26281 A (GENVEC INC ;CORNELL RES FOUNDATION INC (US)) 29 August 1996 see example 7 ---	1,4,6-8, 10,11 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search

14 April 1998

Date of mailing of the international search report

123.04.98

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentkantoor 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Cupido, M

INTERNATIONAL SEARCH REPORT

Interr	nal Application No
PCT/US 97/21494	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. GALL ET AL: "Adenovirus type 5 and 7 capsid chimera: Fiber replacement alters receptor tropism without affecting primary immune neutralization epitopes" JOURNAL OF VIROLOGY., vol. 70, no. 4, April 1996. pages 2116-2123, XP002050655 see the whole document ---	1,4,6-8, 10,11
P,X	WO 97 12986 A (CORNELL RES FOUNDATION INC) 10 April 1997 see page 15, line 1 - line 7 -----	1,2,13

1

INTERNATIONAL SEARCH REPORT

Int'l. application No.

PCT/US 97/21494

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 11 to 13 because they relate to subject matter not required to be searched by this Authority, namely:
Although these claims are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the adenoviral vector
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern	nal Application No
	PCT/US 97/21494

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626281 A	29-08-96	AU 4980496 A CA 2213343 A EP 0811069 A	11-09-96 29-08-96 10-12-97
WO 9712986 A	10-04-97	NONE	